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THERAPEUTIC CONSIDERATIONS AND CONTROVERSIAL ISSUES IN THE MODERN MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION*

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Adequate care for the patient suffering from acute coronary occlusion is one of the most urgent problems in present day therapeutics. Until several years ago, the therapy for this outstanding affliction of our time consisted of little more than the use of morphine and prolonged bed rest. In 1934, Sir Thomas Lewis[15] stated that "treatment of this grave condition is necessarily slight. . . . The patient is nursed in bed as a case of grave cardiac failure . . . for at least eight weeks, even in the milder cases, and during the whole of this period he is to be guarded by day and night nursing and helped in every way to avoid voluntary movement or effort." This regimen commonly referred to as "masterful inactivity" was routinely employed in all cases of acute myocardial infarction until sharply criticized in 1944 by Harrison,[11] Dock[4] and others. As a result of these publications, the evil sequelae of prolonged and complete bed rest have gained wide recognition; the prescribed period of such confinement has been drastically reduced and specific measures to prevent untoward effects from necessary restriction in body movement, have been adopted. To obviate some of the harm of strict bed rest, Levine[14] has advocated the sitting position in a chair with the feet dependent for varying portions of the day, beginning not later than the first week of the attack. An even more drastic departure from the rigid restrictions of activity hitherto practised, has been the recommendation that ambulation be instituted after only 2 weeks of bed rest[13].

In recent years it has become a universal practice to give oxygen to patients with acute myocardial infarction because this agent has been reputed to relieve pain, restlessness and dyspnea, and to reduce the size of the resultant infarct. Improvement in therapy has also been sought in the use of drugs which allegedly dilate the coronary arteries and increase the supply of oxygen to the myocardium. Among the commonest of these have been the xanthines, the nitrites, alcohol and papaverine. Anticoagulants are now widely employed as standard procedure in the treatment of acute myocardial infarction as a result of the recommendation in 1948 for their routine use when no contraindications exist[33]. The need for careful clinical and

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laboratory control when these drugs are administered has also made hospitalization a routine requirement. To combat shock, Paredrine, Neosynephrine, mephentermine and other pressor agents are undergoing trial in an attempt to increase blood pressure without accelerating the heart rate. Small transfusions of blood or plasma and intra-arterial transfusions have also been employed in an effort to influence favorably the shock syndrome.

It is thus apparent that the days of "scientific neglect" have been gradually replaced by a positive therapeutic program which is considered to have improved significantly the prognosis in this disease. This presentation will attempt to evaluate critically certain of the specific measures now employed, to analyze the indications for their use, to point up the dangers of overtreatment, and to emphasize the fallacy in preventive therapy which disregards the fundamental requirement of adequate rest for the heart.

MORPHINE. In the treatment of the acute attack the relief of pain occupies first consideration and for this, morphine and other opiates have no equal. When discomfort is extreme, prompt relief may be obtained by careful intravenous administration of 15 mg. of morphine diluted in 5 to 10 cc. of sterile water. In the past, light anesthesia was occasionally employed when morphia was ineffective. Harlow Brooks[3], in 1929, reported that his administration of chloroform in several cases "killed no patients" but gave "relief of suffering" when morphine seemed powerless. Such procedure, obviously unacceptable today, can often be matched in its relief of pain by the intravenous administration of morphine. In acute coronary thrombosis this drug increases the efficiency of the heart indirectly by relieving pain and dyspnea, thereby improving pulmonary ventilation, decreasing metabolic rate and reducing cardiac work. In spite of its wide use, little is known of the effects of morphine on the coronary arteries. A dilating effect has been described in a few studies on isolated human and dog hearts but clinical confirmation of this action has not thus far been obtained. In experiments in our laboratory[21], morphine was actually found to exert no significant effect on the electrocardiographic response to standard exercise (Master two-step test) in patients with angina pectoris although it did prevent the onset of pain. In these respects, it was strikingly similar to alcohol ingested in the form of Scotch or Rye whiskey. As a result of its vagal stimulation, morphine presents at least the theoretical danger of inducing coronary vasoconstriction and of rendering the heart muscle susceptible to ectopic ventricular rhythms[7]. A real danger resides in its tendency to depress or paralyze the respiratory center and frequently to induce vomiting and retching which add to the circulatory strain. Due to its constriction of smooth muscle, severe constipation and urinary retention may give rise to distressing symptoms. The use of morphine, therefore, like the employment of bed rest, quinidine or anticoagulant drugs in acute myocardial infarction, is associated with a calculated risk. As with these forms of therapy, its administration should be individualized with due consideration of the indications, contraindications, optimum dosage and route of injection in each case. Consequently, it should not be given routinely as soon as the diagnosis of myocardial infarction is made. Mild pain can often be controlled by Demerol or codeine and in some cases, even these are unnecessary. On the other hand, when pain is extreme, as much as one grain of morphine in divided doses may be required over a period of a few hours. Dilaudid, a synthetic drug related to morphine, is favored by some

because it produces vomiting much less frequently and has proportionally more analgesic and less soporific and respiratory depressant effect.

OXYGEN. When pain is severe and intractable, some relief is often afforded by the administration of high concentrations of oxygen. Such relief is more likely to occur in those cases in which cardiac damage and circulatory derangement have resulted in a secondary generalized arterial anoxemia. The administration of oxygen in these instances may relieve dyspnea and cyanosis as well as cardiac pain and may tide the patient over the initial crucial stages of the attack. The diminution in the work of the heart and increased supply of oxygen for the myocardium may conceivably reduce the size of the resultant infarct in subjects with well developed collateral coronary circulations previous to complete occlusion. On the other hand, although oxygen is employed almost routinely, like morphine and anticoagulant drugs, in acute myocardial infarction, there is no clear evidence to support the view that such therapy is justified in the absence of pulmonary edema and subnormal oxygen saturation of the arterial blood. The question as to whether or not hyperoxygenated blood is capable of influencing local myocardial anoxia in patients with uncomplicated myocardial infarction, has not been satisfactorily answered. Clinically, we have not observed benefit in the control of pain in such cases or in others suffering severe paroxysms of angina pectoris even with inhalation of 100% oxygen[20]. In normal animals which admittedly have no functional collaterals, administration of oxygen has proved valueless in experimental occlusion[31]. In other studies[29] on anesthetized dogs, however, it has been shown using platinum electrodes, that there is a statistically significant increase in available oxygen in border zones surrounding areas of infarction after pure oxygen breathing. Fifty percent oxygen proved greatly inferior to pure oxygen in achieving favorable results. These observations support the belief that inhalation of high concentrations of oxygen may reduce the extent of muscle necrosis resulting from coronary occlusion in man. On the other hand, in the anesthetized animal, one does not encounter the psychogenic influences evoked by the administration of oxygen in the human subject afflicted with coronary thrombosis. Administration of oxygen to most patients carries the implication that they are critically ill. When placed in an oxygen tent, some patients develop a sense of claustrophobia. They cannot be easily nursed or satisfactorily fed. Administration of oxygen by nasal catheter frequently leads to irritation or inflammation of the pharynx which cause hacking and coughing, both undesirable efforts. The use of a mask often produces a sense of suffocation and a state of anxiety. Such factors undoubtedly contribute to the total work of the heart and, therefore, are likely to nullify or even overbalance any advantages to be gained from the relatively little additional oxygen which can be added to the blood in patients with uncomplicated myocardial infarction. This is certainly true when oxygen is administered by tent since under optimum conditions a concentration of only 40% can be achieved in this manner. At this concentration, only 1.6 cc. of oxygen can be added to each 100 cc. of blood. Nearly twice this amount can be added if the patient inhales 100% oxygen[2]. Hence, if oxygen is to be administered at all to patients with uncomplicated myocardial infarction, it would appear preferable to use a mask rather than an oxygen tent.

In patients with pulmonary edema or shock, the anoxia may be severe. In these cases, oxygen therapy is mandatory to combat the general effects of

anoxia on the body, as well as to supply additional oxygen to the myocardium. On the other hand, in the patient without pulmonary edema or shock, the degree of anoxia is mild and of no importance to the body as a whole. The sole purpose of oxygen therapy in this group of patients would be the provision of greater amounts of oxygen to ischemic areas of the heart. In order to determine whether the administration of 100% oxygen is capable of influencing anoxia solely confined to a portion of the myocardium, the effect of this therapy on the electrocardiographic response to standard exercise using the Master two-step test, was studied by the authors[20] in a number of patients with angina pectoris. Control studies were first performed with the patient simply breathing room air although wearing an oro-nasal oxygen mask. The tracings obtained were compared with those recorded in an identical manner but with the patient breathing 100% oxygen. The mask was applied 5 minutes before the test and was worn continuously throughout the period of exercise and for the 10-minute period thereafter. It was found that the administration of 100% oxygen did not prevent the RS-T segment and T wave changes induced by standard exercise and failed to hasten the disappearance of these manifestations of myocardial anoxia. The administration of 100% oxygen, moreover, failed to prevent the onset of anginal pain or to influence its duration.

It is concluded, therefore, that oxygen should be freely employed in acute myocardial infarction when an indication for its use is recognized or even suspected. Its continuation, however, should be based on evidence of objective or subjective improvement of the symptom for which it was administered. It should be remembered that the indiscriminate use of oxygen may contribute nothing to the patient's ultimate recovery and yet add considerably to his anxiety and discomfort during the most acute phase of the disease. Consequently, its employment may result in more harm than good in the individual case. Certainly no basis can be found for the use of the oxygen tent in the uncomplicated case of acute myocardial infarction. For the latter, even the high concentrations obtainable with a mask have questionable value, but if oxygen is to be used at all, only this method of administration should be considered.

ANTICOAGULANTS. Following the report[33] of the committee of the American Heart Association, which recommended the use of anticoagulant drugs in the treatment of coronary thrombosis, many investigators have confirmed the value of heparin and Dicumarol in reducing the incidence of thromboembolic complications in this disease and the mortality resulting therefrom. At present there seems to be little doubt that in severely ill patients the anticoagulants have an important place in treatment, but it is more difficult to justify their routine use in all cases of coronary thrombosis. The claim has been made that clinical experience is replete with examples in which disabling or fatal thromboembolism has occurred unexpectedly in the course of relatively mild attacks of acute myocardial infarction[32]. This view is in accord with statements found in almost all textbooks of cardiology which declare empirically that the outcome from acute coronary thrombosis is unpredictable because of the constant threat of sudden unexpected death even for persons convalescing favorably. In an attempt to determine the frequency of thromboembolism as a cause of disability and death in relatively mild cases of acute myocardial infarction, the effect of conventional treatment without the use of anticoagulants was studied in 489 patients who sustained an "uncomplicated" first attack of the disease[25,28]. The serious

prognostic signs enumerated for the purpose of selection were a history of previous infarction, intractable pain, severe or persistent shock, cardiac enlargement, gallop rhythm, heart failure, arrhythmias and other states predisposing to thrombosis. In the good risk group where none of these factors were present on the day of admission to the hospital, the mortality was only 3.1% as compared with 60% in the group showing one or more of these unfavorable signs. Similarly, the frequency of thromboembolic complications in the 2 prognostic categories was 0.8% and 10.6% respectively. When allowance was made for deaths which obviously could not have been prevented by Dicumarol it became evident that in the "good risk" group the theoretically preventable mortality with this drug could not have exceeded 1.0%. In fact, among good risk patients surviving 48 hours from the time of admission, the subsequent death rate from all cardiovascular complications during hospitalization was only 1.2%. These findings, therefore, do not reflect the formidable risk of sudden death, claimed to exist by many authorities even in the course of mild attacks of this disease. The data, furthermore, do not confirm the view that thromboembolism is an obviously significant cause of disability and death among such milder cases.

Inasmuch as Dicumarol has, since 1947, become one of the most common causes of death due to drugs[6], its employment for mild attacks of coronary thrombosis in which the risk of thromboembolism is small, does not appear warranted. Major hemorrhage occurred in 1.9% of over 9000 patients given Dicumarol according to a review of the literature[5] and in 2% of 15,500 patients treated with Dicumarol and heparin by 136 physicians responding to a questionnaire[17]. In a recent survey[26] 228 cardiologists and internists reported a total of 122 deaths caused by hemorrhage from heparin or Dicumarol in the treatment of myocardial infarction. The true frequency of death from hemorrhage induced by heparin or Dicumarol will not be accurately known until more extensive statistical studies based on necropsy findings, are at hand. Although most reports of hemorrhagic complications in the literature are those of skilled investigators in large medical centers, it must not be overlooked that general practitioners and not specialists treat the vast majority of patients with acute coronary thrombosis. From all available data, therefore, no acceptable basis for the use of anticoagulant drugs can be found in patients sustaining an uncomplicated first attack. Similar findings and conclusions have recently been reported by Papp and Smith[18] Baer and associates[1], Littman[16] and others.

It has been maintained that old age provides a special indication for the use of anticoagulant drugs in cases of acute myocardial infarction. The patient over the age of 60 is commonly regarded as more vulnerable than the younger patient who has sustained an attack of similar severity. Recent studies[27] indicate that no justification exists for this concept. Although statistically there is a relatively higher incidence of serious attacks among older patients, the prognosis for a severe attack or a mild one appears to be unaltered by age. The initial clinical appearance of the patient would, therefore, seem to constitute the best index to his future course and the deciding factor regarding the need for anticoagulant therapy.

Some evidence suggests that anticoagulants may have additional life saving actions beside that of preventing thromboembolism. The belief is held by some that these agents prevent congestive failure, sudden ventricular fibrillation and asystole by preventing clotting in the coronary lumen. Gilbert and Nalefski[8] have suggested that the

favorable results observed from the use of anticoagulant drugs in cases of acute myocardial infarction and angina pectoris may be primarily the result of an increase in coronary blood flow. Graham and associates[10], however, in reporting marked relief of anginal symptoms in patients receiving periodic injections of heparin, attribute the beneficial response to the profound effect of this drug on lipoprotein metabolism. Our own studies[23] with heparin have failed to demonstrate either subjective improvement in anginal symptoms or favorable influence on the electrocardiographic response to standard exercise. The recent report of Gilchrist[9] offers a possible explanation for the unexpectedly large benefits reported from the use of anticoagulant drugs. Gilchrist observed that the early and efficient use of heparin and Dicumarol or Tromexan appears to influence favorably the outcome of the shock syndrome. Deaths from shock were stated to have been reduced from 15% to 4% as the result of therapy. Gilchrist suggests that the early employment of heparin, in addition to the more slowly acting anticoagulants, may limit the spread of multiple thrombotic extensions in and through the zone of demarcation separating the necrotic from the adjoining healthy muscle. Control of the thrombotic tendency may thus prevent an advance in the vicious cycle of thrombosis, infarction and hypotension. If these findings are confirmed, the current practice of administering Dicumarol or Tromexan alone without the immediate use of heparin must be viewed as falling far short of attaining optimum protection from anticoagulant therapy. In any case, it would appear that the latter should be reserved for the more serious instances of acute myocardial infarction in which the frequency of complications justifies the risk.

HOSPITALIZATION. The wide employment of anticoagulant drugs in acute coronary thrombosis has been associated with a risk commonly overlooked. In order to institute treatment without delay many patients are rushed to the hospital shortly after the onset of their clinical attack despite the fact that the highest death rate in this disease prevails during the first 48 hours. Since these early deaths are the result of ventricular fibrillation, cardiac asystole, shock or congestive heart failure and are unrelated to thromboembolism, they almost certainly cannot be prevented by anticoagulant drugs. The desire to save the small proportion, who may die from thromboembolism after the first week, may therefore jeopardize the chances for survival of the much larger segment of coronary cases known to die from other causes during the first 2 days. For many patients, being jostled in an ambulance or admitting office, then subjected to the psychic trauma of a hospital room and bed and of being placed in an oxygen tent, often when oxygen is entirely unnecessary, and being repeatedly punctured for prothrombin and coagulation times, hardly constitutes optimum management during this early critical period. In most instances, any form of treatment deemed necessary can be initiated in the patient's own home and removal to hospital can be accomplished if indicated, when this critical period has passed.

VASODILATORS. Many drugs reputed to have "vasodilator" action, have been employed in the treatment of coronary disease. A wide divergence of authoritative opinion exists, however, regarding the value of most of these agents. Disagreement has stemmed from the fact that such a drug cannot be recognized simply by an ability to increase coronary blood flow. This is because myocardial anoxia itself is the most potent of known coronary vasodilator agencies[30]. A drug may increase coro-

nary flow through the undesirable effect of increasing cardiac work, decreasing arterial oxygen tension or decreasing myocardial efficiency. Such unfavorable action can be recognized by a decrease in oxygen content of the blood in the coronary sinus together with increased coronary flow. A favorable drug in coronary disease is one which increases coronary venous oxygen saturation and cardiac efficiency with concomitant decrease in cardiac work and coronary vascular resistance. Such a drug can be evaluated only by simultaneous quantitative measurements of coronary blood flow, myocardial oxygen consumption, cardiac output and mean arterial blood pressure in a normal animal. From these data, changes in cardiac work and efficiency can be estimated. According to these criteria[30], amyl nitrite, nitroglycerine and papaverine are desirable, tetraethyl ammonium chloride and spinal anesthesia are without significant effect and aminophylline and Coramine are undesirable. Such observations in normal animals, however, may not correlate with the effects of these drugs in human coronary disease. In previous studies it has been found possible to evaluate the action of various drugs on the coronary circulation and/or myocardium in man by means of an objective technique[19-23]. This method requires the study of selected patients with coronary disease who exhibit upon repeated tests under standard conditions, a relativelv constant, positive response to the Master two-step test. The difficulty in obtaining cases suitable for such study can be appreciated from a 4-year experience in screening over 3000 patients with coronary artery disease. Of this number only 52 subjects have qualified as satisfactory for this type of investigation. By this method we have studied the effect of a large number of drugs on the electrocardiographic response to standard exercise. Among these agents were nitroglycerine, papaverine, whiskey, aminophylline, morphine, khellin, Roniacol, octyl nitrite, Peritrate, Priscoline, tetraethyl ammonium chloride, 100% oxygen, cortisone and heparin. It is apparent that this method of study can only indicate whether or not the net effect of a drug upon the heart is beneficial for no information is obtained regarding its mode of action. From these observations the following drugs were found to be without value as judged from the post-exercise electrocardiograms: whiskey, khellin, Roniacol, Priscoline, tetraethyl ammonium chloride, inhalation of 100% oxygen, cortisone and heparin. Only slight beneficial effect was noted from the use of octyl nitrite, and aminophylline even in large dosage. Nitroglycerine, papaverine in doses of 130 mg. intravenously and 0.2 to 0.5 gm. orally and Peritrate (pentaerythritol tetranitrate) evoked dramatic response in a number of the patients studied. With the favorable drugs the necessity for individualizing dosage was apparent throughout. A number of paradoxical responses were noted with nitroglycerine as a result of increased sensitivity to usual doses of the drug[24]. In these patients, the exercise test produced an increase in the degree of ST segment depression and T wave inversion when 0.4 mg. of nitroglycerine was administered 5 minutes before exercise. The reverse was the case with 0.2 mg. Further observation has shown that these paradoxical responses result from venous pooling in the lower extremities induced by nitroglycerine. The unfavorable response is prevented by elastic bandages applied to the lower extremities or by decrease in the dosage of nitroglycerine. The paradoxical effect of nitroglycerine in these cases was not found to be due to fall in blood pressure although in some instances this action

appeared implicated as well. The danger in employing nitroglycerine in acute myocardial infarction may stem from the combined effects of the drug in reducing blood pressure and diminishing venous return to the heart. It is possible nevertheless that the administration of nitroglycerine in amounts varying between 0.15 and 0.3 mg. every 2 to 3 hours may be of considerable value in improving collateral circulation during convalescence from acute myocardial infarction[12]. Papaverine would appear more desirable during the first few days following the attack because of its additional action in preventing ectopic rhythms. It is best administered in these cases subcutaneously at 4 to 6-hour intervals in the dosage of 0.1 to 0.2 gm. After 1 or 2 days, it may be given orally and after a week, it may be replaced by nitroglycerine in small divided doses. Peritrate, because of its prolonged action, may in small dosage, prove to be the drug of choice when coronary vasodilatation is sought during convalescence from acute myocardial infarction. In our hands it has proved to be the best agent thus far employed for prophylactic therapy in angina pectoris (10 to 20 mg. T.I.D.)

BED REST. One of the major problems in the management of patients with myocardial infarction involves the decision concerning the duration and rigidity of restriction of activity. The present trend in care of patients with coronary disease is a liberalization of the rigid restrictions of activity hitherto practiced. The evidence to date would seem to indicate that there is every advantage in prolonged restriction of activity, but little advantage in prolonged rigid rest in bed. The cardiac work which is roughly the product of output and blood pressure, tends to be less in the sitting than in the recumbent position. The "chair" treatment advocated by Levine[14] in which the goal is to have the patient out of bed as much of the day as is comfortable from the beginning of the illness, cannot, therefore, be challenged on the grounds of failing to give maximum rest to the heart. The sitting position in the chair obviates some of the well known harmful effects of strict bed rest; it appears to have beneficial effects on the psychological state of the patient and facilitates the rehabilitation process. In Levine's series the majority of patients were out of bed for 1 to 2 hours the first day and for increasing intervals thereafter. One may question the wisdom of utilizing chair treatment during the first few days of the illness. Considerably more than one half of all the deaths in this disease occur during the first 2 days. Many of these happen suddenly and unexpectedly as a result of cardiac standstill, ventricular fibrillation, shock or congestive heart failure. Even in the mildest cases, a high proportion of all deaths occur suddenly within the first 48 hours[25,28]. For this reason it would seem best that the patient be disturbed as little as possible during the first few days of his illness. Strict bed rest would appear to be more desirable during this early critical period following which armchair treatment might be more safely instituted. This does not mean that the patient should be placed flat in bed since the semi-recumbent or sitting position is more desirable in the absence of shock. Although some have advocated early ambulation after 2 weeks of bed rest[13], permission to walk probably should not be granted before the end of the third week even in the milder cases.

TRANSFUSIONS, VASOPRESSOR DRUGS AND DIGITALIS. If further improvement in the prognosis of acute myocardial infarction is to be obtained, the problems involved in the prevention and treatment of the severer grades of shock and congestive heart failure must be

solved. It has been claimed that protracted shock, if survived predisposes to a greater or less degree of congestive failure at an early date[9]. Evidence has been presented which suggests that the prompt and efficient treatment of cardiogenic shock may well be the means of preventing the subsequent development of congestive heart failure. The latter may, therefore, be anticipated on occasions and necessary measures taken in advance. Cardiogenic shock is a complex entity in which a reduced cardiac output is not uncommonly associated with evidence of pulmonary congestion, a sign indicative of a venous return in excess of that which the left ventricle can accommodate. It is a condition which requires energetic treatment aimed at the restoration of arterial pressure to a level consistent with an adequate coronary flow. The employment of blood transfusions for this purpose presents the risk of pulmonary edema because of the dangerous potentialities of increasing blood volume in the presence of a failing heart. Nevertheless, in selected cases, transfusions of blood or plasma have occasionally proved beneficial. A need exists for a pressor drug which increases peripheral resistance and augments coronary flow without stimulating metabolism, decreasing cardiac output or initiating serious arrhythmias. Epinephrine which increases the tendency to ectopic rhythms is undesirable. In serious cases of shock, desoxyephedrine, ephedrine, norepinephrine, Paredrine, Neosynephrine or mephentermine appear worthy of trial. Paredrine, Neosynephrine, norepinephrine and mephentermine have the advantage of raising blood pressure without increasing cardiac rate, or causing significant central stimulation as does epinephrine or ephedrine. Such therapy combined with rapid digitalization may be found to reduce the mortality from severe cardiogenic shock. On theoretical grounds, some physicians hesitate to use digitalis in the presence of a recent infarct fearing that it may favor rupture of the ventricle, induce serious arrhythmias, enhance the clotting tendency or dislodge cardiac thrombi. Most authorities, however, do prescribe digitalis for the treatment of heart failure even in the first few days after myocardial infarction although often in somewhat smaller than usual dosage. In spite of the various measures employed, however, the inadequacy of treatment for the shock syndrome accompanying acute coronory thrombosis continues to present a major obstacle to recovery in this disease.

In summary, it would appear that perhaps some 40% of all cases of acute myocardial infarction require little more than sedation for pain and medical guidance as to the duration and degree of restriction of activities. In these patients nature requires little assistance from the attending physician to bring about uneventful recovery. In the remaining complicated cases, however, careful evaluation of the signs and symptoms in the individual patient should dictate the specific measures most likely to influence favorably the natural course of the disease. The administration of drugs or procedures without clear indication should be avoided since there is no disease in which overtreatment or disregard of physiological concepts can prove more disastrous.

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OBSERVATIONS ON THE ERYTHROCYTE SEDIMENTATION RATE IN CONGESTIVE HEART FAILURE†‡

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The erythrocyte sedimentation rate (ESR) is generally considered to be normal or near normal in congestive heart failure. As early as 1898, Müller[21] reported that a decrease in the ESR occurred in cardiac decompensation, but despite the fact that in the intervening years many investigations have been directed toward the characterization of the ESR in a number of other clinical conditions, the effect of congestive heart failure on this test has not been subjected to extensive analysis. Indeed, other than the observations of Wood[37] on the ESR in 22 cases of congestive failure of varied etiology, adequate data are not available in the literature. Nonetheless, it is often taught that the ESR is normal in heart failure, and a number of statements to this effect may be found in the literature[3,4,12,33]. In order, therefore, to define more critically the validity of the prevailing concepts concerning the ESR response to congestive cardiac failure, the following study was undertaken.

Methods. Patients admitted consecutively to the male and female wards of the Washington University Medical Service of the St. Louis City Hospital and to the male medical wards of the Homer G. Phillips Hospital with the principal diagnosis of congestive heart failure due to arteriosclerotic heart disease, hypertensive cardiovascular disease, or syphilitic heart disease were included in the study. The only patients excluded were those who presented demonstrable evidence of rheumatic heart disease or of myocardial infarction[15,25,30], acute and chronic infections[3,14,35], pregnancy[14,35], rheumatoid arthritis[2], tumors[3,35], or other conditions[8,11,14,35] known to lead to elevation of the ESR. Also excluded were patients not seen within 24 hours of entry, and those who did not remain long enough for at least 2 ESR determinations.

In addition to a history and physical examination, complete blood counts and urinalyses were available on each patient, and in almost every instance a chest roentgenogram and an electrocardiogram were obtained. The majority of the patients received prophylactic chemotherapy.

For purposes of this study the technique of Wintrobe and Landsberg was employed[36]. Two cubic centimeters of blood were drawn aseptically from an arm vein. In order to avoid venous stasis, tourniquets were not

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used unless necessary; when they were employed, they were released prior to withdrawal of blood. The blood was transferred to tubes containing 1.6 mg. potassium oxalate and 2.4 mg. ammonium oxalate as anticoagulants, and the tubes were inverted to insure adequate mixing. Within 2 hours after collection of each specimen, a Wintrobe calibrated hematocrit tube was filled to the indicated level with thoroughly mixed blood and placed in a suitable rack, so constructed that the tube was held exactly perpendicular to the horizontal. The amount of fall of the column of sedimenting erythrocytes at the end of one hour was recorded, and after the packed cell volume was determined by centrifugation of the tubes at 3000 RPM for 30 minutes, the ESR was corrected for a hematocrit of 45 for females and 47 for males by reference to the standard curves. For the male patients, ESR values up to 9 mm. per hour were considered normal, while a value of 15 mm. per hour was considered the upper limit of normal for females. ESR determinations were made twice weekly during the first 2 weeks of each patient's hospital stay; thereafter weekly determinations were done.

Thirty-eight of the patients studied were suffering from acute congestive failure while 13 had chronic failure. Seven of the patients in the latter group succumbed without regaining cardiac compensation. In the acute failure group, the ages of the patients ranged from 42 to 89. Fourteen patients were white, 24 Negro. Only 4 were females. Of the 13 patients with chronic failure, the youngest was 46, the oldest 87. Ten were white, and there were 7 males in the group.

TABLE 1.—THE ESR IN ACUTE CONGESTIVE HEART FAILURE

Case No.	*Age*	*Sex*	*Race*	*ESR in Acute Stage*	*ESR after Compensation*
1	85	M	N	0	26
2	66	M	N	0	8
3	58	M	N	3	28
4	70	M	N	3	16
5	49	M	W	5	16
6	62	M	N	6	14
7	58	M	W	6	28
8	60	M	N	7	13
9	54	M	N	8	24
10	60	M	N	8	19
11	66	M	N	8	24
12	89	F	W	15*	28
13	62	M	N	10	25
14	73	M	W	10	21
15	72	M	W	11	37
16	74	M	W	13	12
17	79	M	W	14	10
18	51	M	W	15	29
19	79	M	N	15	32
20	60	M	N	16	18
21	52	M	N	18	29
22	46	M	N	20	33
23	78	M	W	21	38
24	65	F	W	22	36
25	66	M	N	23	3
26	61	M	N	24	14
27	58	M	N	24	30
28	73	M	N	25	25
29	38	M	W	25	28
30	75	M	W	28	16
31	53	M	N	28	8
32	59	M	N	29	19
33	42	M	N	30	5
34	77	M	N	30	20
35	45	M	N	32	10
36	35	M	N	33	27
37	62	F	W	39	37
38	71	F	W	41	38

NORMAL

ELEVATED

* Normal value for females

Results. The data collected from the 38 patients with acute cardiac failure are summarized in Table I. Arbitrarily the position of each patient in the table is based on his or her initial ESR during the period of decompensation, those patients with the lowest values being listed first.

It will be noted that Table I is subdivided to indicate those patients whose initial ESR values were normal. Approximately one-third of the cases were characterized by normal ESR values, and in somewhat less than one-third, moderate ESR elevation was observed. The remainder of the patients had distinctly high ESR values.

After compensation had been regained, in only 4 of the patients were normal ESR values recorded. The other 34 exhibited elevations, half of them distinctly high. The distribution of the ESR values in this series, before and after compensation, is shown in Fig. 1.

Thirteen patients in the acute failure group had lower ESR values after recovery than they had at the time of entry. In 4 instances in which the ESR had been high at the outset, normal or near normal values were noted. Two patients had only slight elevation of the ESR initially, and in each case the ESR fell only slightly. In 2 others who had very high ESR readings when admitted, there was a slight fall after recovery but the values still were very high. Finally, in 3 patients, the ESR after compensation was the same or only slightly higher than that found during cardiac failure.

As shown in Table 2, 5 of the 13 patients with chronic, intractable congestive heart failure studied had normal ESR values when they were admitted to the hospital and subsequently during their course. It is significant to point out that all but one of these patients died. In a sixth patient, the ESR was moderately elevated initially and

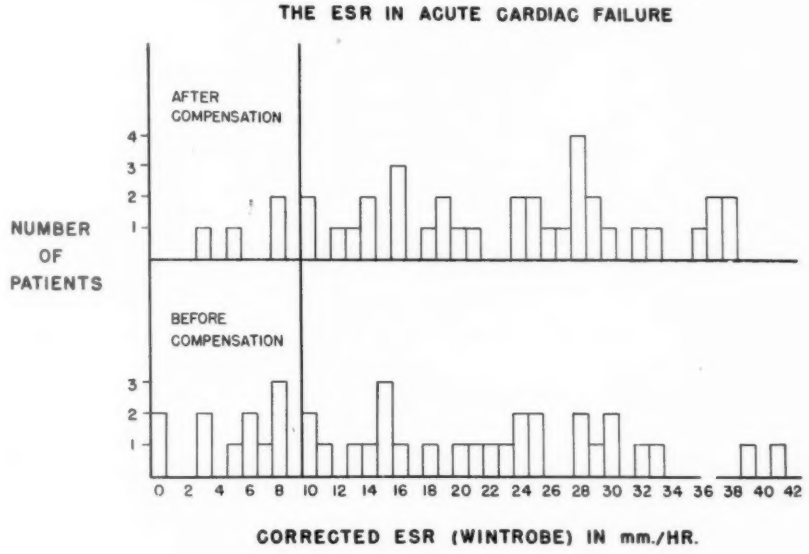

FIG. 1.

fell to normal during the patient's hospitalization, which terminated fatally. The other 7 patients had a high ESR at the time of entry, and a significant elevation persisted. The distribution of initial and subsequent average ESR determinations in the chronic heart failure group is given in Fig. 2.

general hospitals. The predominance of male patients in the study reflects the fact that in one of the 2 institutions, it was feasible to make observations only on males. The only patients excluded were those known to have lesions ordinarily associated with elevation of the ESR, those not seen

TABLE 2.—THE ESR IN CHRONIC CONGESTIVE HEART FAILURE

Case No.	*Age*	*Sex*	*Race*	*ESR on Admission*		*ESR Subsequently*
1	85	M	N		1	4*
2	87	F	W		2	8*
3	54	F	W	NORMAL	4	6
4	87	M	W		6	4*
5	46	M	N		8	0*
6	74	M	W		16	6*
7	60	M	N		28	18*
8	66	M	W		31	35
9	50	F	W	ELEVATED	34	29*
10	74	M	W		37	36
11	55	F	W		39	50
12	69	F	W		43	30
13	59	F	W		46	42

* Patient died

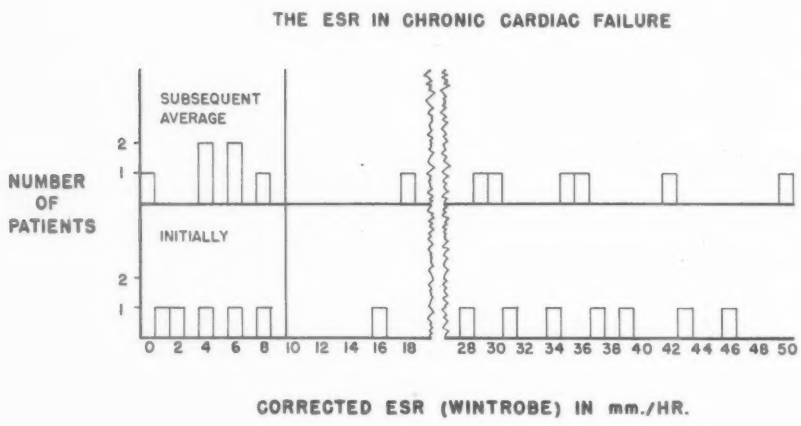
THE ESR IN CHRONIC CARDIAC FAILURE
SUBSEQUENT AVERAGE
NUMBER OF PATIENTS
INITIALLY
2
1
2
1
0 2 4 6 8 10 12 14 16 18 28 30 32 34 36 38 40 42 44 46 48 50
CORRECTED ESR (WINTROBE) IN mm./HR.

FIG. 2.

Discussion. The study herein described was carried out because the available evidence did not seem to afford an adequate basis for the rather widely-held concept that the ESR tends to be normal in the presence of congestive heart failure. The patients included were those admitted consecutively to the medical wards of 2 large

promptly after admission and those whose course was too short to permit at least one repeat ESR determination.

It is likely that some of the patients had inapparent complications or concomitant diseases with which high ESR values are associated, and this possibility must be considered in the interpretation of the results. In view of

the fact that the diagnosis of such complications is a common problem to the clinician, it is of practical interest that the ESR apparently is not in itself an aid in ruling in or out infarction, infection or other complications in patients with heart failure.

The exclusion of patients with rheumatic heart disease requires comment. There is some evidence which suggests that acute rheumatic fever frequently is an unrecognizable concomitant of cardiac failure in patients with rheumatic heart disease[1]. In addition, it has been reported that in patients suffering from acute rheumatic fever, the characteristically elevated ESR falls to normal when decompensation ensues[24,29,37]. In order to avoid the introduction of additional variables which would have further complicated elucidation of the ESR in congestive heart failure *per se*, the rheumatic group was not included.

The collected data indicate that the ESR may be normal but tends to be elevated in both acute and chronic cardiac failure. Normal levels were encountered in the majority of patients succumbing to failure only, but because of the small number of patients in this category, this particular observation must be considered of limited significance. It should be emphasized that after compensation was regained, 21 of the 38 patients who were admitted with acute heart failure had higher ESR values than on admission.

The ESR is determined by a number of physical and chemical factors, not all of which are necessarily operative in a given instance. Thus, among the factors which may influence the ESR, the following may be mentioned: oxygen and carbon dioxide content[28], cholesterol[16,32], total and fractional proteins[5,6,19,27], pH[13,19], erythrocyte charge[13,18,19], and temperature[26,31]. *

The relative role of these various factors in determining the ESR in cardiac failure is not clear, but the fibrinogen content of the blood is probably of major importance[7,9,17,20], a decrease in fibrinogen being associated with retardation of the ESR. Since evidence suggests that fibrinogen production by the liver is maintained unless hepatic damage is of extreme degree[10], chronic passive congestion, except when of great severity, probably does not significantly decrease the fibrinogen content of the blood. This assumption, if valid, is compatible with the findings that the ESR is elevated in most patients with heart failure, and normal only in the most severe, chronic cases, It is in the latter group, with prolonged, intractable failure, that hepatic damage might be expected to be so extensive as to lead to decreased fibrinogen production.

It should also be pointed out, in considering the influences which affect the ESR, that the values for the ESR increase somewhat with advancing age *per se*[23,24]. A large number of the patients in the present series were in their sixth, seventh, or eighth decades, and a few were in the ninth decade; it is possible, therefore, that the factor of age was a significant one in the results obtained. Finally, as yet undefined influences may also bear on the ESR in congestive failure.

The question of why the ESR tends to rise after compensation is regained remains unanswered. Since passive congestion usually results in tissue necrosis, it may be postulated that the absorption of the products of necrosis may play a part in the enhancement of the ESR, in the period immediately after compensation. Although this hypothesis seems reasonable, it is nonetheless speculative. As already pointed out, it is unlikely that alteration in

* A comprehensive review of the factors affecting the sedimentation rate has been published by Nichols[22].

plasma fibrinogen is a contributory factor.

Summary and Conclusions. Determinations of the ESR in 38 patients with acute congestive heart failure, prior to and after compensation was regained, indicate that the majority of such patients exhibit elevated values, not only initially but after recovery as well. Similarly, in a small group of patients with chronic cardiac insufficiency the ESR tends to be high except in those individuals succumbing to heart failure.

Factors which are thought to influence the ESR in heart failure have been reviewed and discussed briefly.

In the presence of heart failure, an elevated ESR value cannot be considered a reliable indication of pathologic abnormalities such as infarction, infection or thrombo-phlebitis.

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CIRCULATORY AND VENTILATORY CHANGES IN CHRONIC RHEUMATIC HEART DISEASE WITH MITRAL STENOSIS*

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STRUCTURAL changes in the lungs of patients with mitral stenosis have been demonstrated both by pathological study[30] and by Roentgen-ray[32]. In addition, alterations in circulation and pulmonary ventilation develop when congestive failure occurs in mitral stenosis. The development of cardiac surgery for mitral stenosis has stimulated interest in the physiological changes associated with this disease. The present report deals with circulatory and ventilatory changes of mitral stenosis and their relation to structural changes in the heart and lung. In addition, some observations have been made concerning the evaluation of patients for mitral valve surgery.

Methods. MATERIAL. This report concerns 13 adult patients from the University Service of the Grace-New Haven Community Hospital in whom a diagnosis of rheumatic mitral stenosis had been made and who were being considered for mitral valvulotomy.

TECHNICAL PROCEDURES. Following a general clinical evaluation which included roentgenograms and electrocardiograms, each patient while in a basal state was subjected to cardiac catheterization under fluoroscopic control. With the patient supine, pressures were recorded in the heart, pulmonary artery and capillaries, and samples of mixed venous blood were obtained. A timed sample of expired air was collected in a Douglas bag, and arterial blood samples were obtained while the patient was breathing room air and after breathing pure oxygen for 5 minutes. Blood pressures with the zero point at table level were recorded by means of a Hathaway multiple channel recording apparatus. All blood gas analyses were done in duplicate by the Ordway modification of the method of Roughton and Scholander[29]. Saturations were calculated using values for blood oxygen content from which the amount of oxygen in physical solution had been subtracted. In this laboratory the normal arterial blood oxygen saturation is 95% or higher, although from 91.5 to 95% is a borderline range[27]. The volume of the expired air sample in the Douglas bag was measured, and the sample analyzed for oxygen content in the Scholander micro-gas analyzer[33]. The oxygen consumed by the patient in one minute was calculated according to a standard method[3].

Pulmonary function studies done in each patient consisted of an estimation of lung volumes and maximal breathing capacity using a Warren-Collins Respirometer, and functional residual capacity estimated by a modification of the method of Darling, Cournand and Richards[9].

CALCULATIONS. Systemic blood flow was determined by using the Fick principle[12]. Formulas for the calculation of shunts have been described earlier[18]. They are based on Lundsgaard and Van Slyke's concept of an α or "net" right-to-left shunting of mixed venous blood into the pulmonary vein without passing through ventilated capillaries, and an L or "lung" factor representing hemoglobin passing through ventilated capillaries without becoming fully saturated with oxygen[26]. The former is expressed as a percentage of total systemic blood flow, the latter as a per cent of total hemoglobin. The formula used here for calculating the "L" factor was developed by Ordway[29].

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The blood flow and shunt formulas are:

$$1.\quad \dot{Q}b = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}$$

$$2.\quad \alpha = \frac{CL\bar{c}O_2 - CaO_2}{CL\bar{c}O_2 - C\bar{v}O_2}$$

$$3.\quad L = \frac{(CaO_2o - CaO_2) - (TbO_2o - TbO_2) - (CbdO_2o - CbdO_2)}{TbO_2}$$

When $\dot{Q}b$ = systemic blood flow in liters/minute; $\dot{V}O_2$=oxygen consumption in cc./minute; CaO_2=arterial blood oxygen content in volumes % x 10; $C\bar{v}O_2$=mixed venous blood oxygen content in volumes % x 10; α="net" right-to-left shunt of blood resulting in an arterial oxygen saturation deficit not overcome by breathing pure oxygen, and expressed as a per cent of systemic flow; $CL\bar{c}O_2$=pulmonary capillary blood oxygen content in volumes % x 10. This value is derived from the expression: $TbO_2 + CbdO_2 - L\ (TbO_2)$; L=per cent of hemoglobin passing through aerated pulmonary capillaries which, due to faulty ventilation or diffusion is not fully oxygenated while breathing room air but becomes saturated while breathing pure oxygen[26,2]; Tb_{02}=total corrected oxygen capacity of the blood in volumes % x 10; Cbd_{02}=oxygen physically dissolved in blood in volumes % x 10.

The subscript $_0$ refers to functions estimated while the patient breathed pure oxygen.

The mitral valve area was calculated according to the method described by Gorlin and Gorlin[14]. Resistance in the pulmonary vascular tree was estimated by the formula of Aperia[1]. Formulas for mitral valve area[14] and pulmonary vascular resistance[1] are:

$$4.\quad MVA = \frac{MVF}{31\sqrt{\text{"PC"} - 5}} \quad \text{if,}$$

$$5.\quad MVF = \frac{\text{cardiac output in cc. per minute}}{\text{diastolic filling period in seconds per minute}}$$

When MVA = mitral valve area in square centimeters; MVF = mitral valve flow in cc./second; 31 is an empirical constant; PC = pulmonary capillary pressure in mm.Hg; 5 is an assumed left ventricular diastolic pressure. The expression "cardiac output" is used here because it was used by the authors of the formula. Otherwise, in the report, the expression "rate of systemic blood flow" will be used since, in terms of the Fick principle, it is less ambiguous than "cardiac output."

$$6.\quad \text{Resistance in dynes-seconds-centimeters}^5 = \frac{\text{Pressure differential}}{\text{Systemic flow, cc./sec.}} \times 1332.$$

Results. CLINICAL FINDINGS. The clinical findings in the 13 patients studied are summarized in Table 1. One individual (V.M.) was studied twice and is listed as case numbers 2a and 2b. Nine of the 13 patients were females. The ages of the patients at the time of study ranged from 19 to 46 years. Two of the 13 patients (cases 9 and 12) had no symptoms referable to the cardio-pulmonary system, while, in all the rest, symptoms had been present for one to 16 years. The severity of symptoms was moderate or marked in 6, and slight in 5 of the patients. Six individuals were taking a digitalis preparation at the time of study, and one of these (case 2a) was subsequently restudied (case 2b) 3 months after digitalis had been discontinued.

All the individuals studied had mitral stenosis. Clinically this was the only valvular lesion present in 3 patients, while in addition, 8 had signs of mitral insufficiency, 4 had evidence of aortic involvement (aortic stenosis and/or insufficiency), and 4 had Graham-Steell murmurs. There was some cardiac enlargement by Roentgen-ray in all but one individual (case 8). Six of the patients had shift of the electrocardiographic axis to the right and one (case 4) had left axis shift. The latter patient had evidence of aortic stenosis and mitral insufficiency in addition to mitral stenosis. One patient (case 3)

TABLE 1.—CLINICAL DATA

Case No.	*Patient*	*Sex*	*Age Yrs.*	*Age of Onset Yrs.*	*Duration of Symptoms*	*Severity*	*Valve Lesions*	*Time on Digitalis Yrs.*	*Roentgenogram*	*ECG Axis & Rhythm*
1	ML	F	42	19	15	Slight	MS	15	Mod. LA, RV enlargement, Pulmonary vessels full	N
2a	VM	F	32	?	3	Slight	MS	2	Marked LA, RV enlargement	N
2b	VM	F	32	?	3	Slight	MS	0*	Marked LA, RV enlargement	N
3	DM	F	39	11	16	Marked	MI, MS, AI, AS	3	Moderate LA enlargement, Right mediastinal node	N
4	LW	M	42	21	5	Slight**	MI, MS, AI	½	Marked general enlargement	Moderate LAS, Aur. fibrillation.
5	JM	F	35	13	6	Marked	MI, MS, PI (rel.)	6† (3 days)	Marked general enlargement Aneurysm L. Pul. artery	Slight RAS Aur. fibrillation
6	DL	F	31	21	2	Moderate	MI, MS PI (rel.)	1	Marked LA, LV, RV enlargement Pulmonary congestion	Slight RAS Aur. fibrillation
7	PF	M	40	10	2	Marked	MI, MS	0	Marked general enlargement	Moderate RAS, NSR
8	JV	F	25	7	5	Slight	MS, AI	0	Indeterminate	N
9	AE	M	26	15	0	0††	MS, MI	0	LA, RV enlarged, calcific mitral valve	Marked RAS, NSR
10	IW	F	46	?	6	Moderate	MS, MI, AS	0	Marked LA, LV, RV enlargement Pulmonary vessels full Nodular densities	N
11	BS	F	32	?	12	Marked	MS, MI, PI (rel.)	0	Marked LA, RV enlargement	Marked RAS, NSR
12	DK	M	19	2	0	0	MS, PI	0	Slight general enlargement Pulmonary vessels full	Slight RAS, NSR
13	RM	F	37	15	5	Slight	MS	0	Minimal LA enlargement	N

* This patient had discontinued the use of digitalis 3 months previously.

** The severity of symptoms referable to cardiac function was slight, however, the patient was partially disabled because of embolic phenomena.

† Digitalis had been used for 6 years, then discontinued for 2 months, and reinstated in a single digitalizing dose followed by a maintenance dose 3 days before this study.

†† This patient had no symptoms referable to cardiac function, but had had embolic phenomena and subacute bacterial endocarditis.

KEY

Valve lesions: MS, MI, AS, AI, PI = Mitral stensois, mitral insufficiency, aortic stenosis, aortic insufficiency, and pulmonic insufficiency respectively.
Roentgenogram: LV, LA, RV = Left ventricle, left atrium, right ventricle respectively.
Electrocardiogram: N, LAS, RAS, NSR = Normal, Left axis shift, Right axis shift, and normal sinus rhythm respectively.

also had pulmonary sarcoidosis, and 2 had had peripheral embolic phenomena (cases 4 and 9) in one (case 9) associated with subacute bacterial endocarditis which had been cured before the time of study.

PHYSIOLOGICAL STUDIES. The physiological observations in the 14 studies are given in Tables 2, 3, 4, and 5. In only 4 studies was an abnormally low arterial blood oxygen saturation observed (Table 2) although 3 additional cases fell in the borderline area between 91.5% and 95%. The patients with abnormally low arterial oxygen saturation (cases 3, 6, 7, 11) had moderately or markedly severe symptoms. In this group, the deficit of arterial oxygen saturation (except in case 11 where a slight α factor is present) could be overcome by breathing pure oxygen indicating that the deficit was related to an increased "L" factor. In the present study, only one patient (case 8) had a mixed venous blood oxygen saturation above 70%. In our experience the normal resting mixed venous blood oxygen saturation does not fall below 70%.

The systemic blood flows (Table 3) tended to be low in relation to body surface area except in cases 2a, 8 and 12. The values were somewhat lower in the digitalized group (cases 1, 2a, 3, 4, 5, 6) than in the non-digitalized group. The stroke volume was below 50 cc. in 5 cases and above 60 cc. in 4 cases. Assuming the normal stroke volume to be above 60 cc.[3], the remaining cases are probably borderline in this respect. There was no significant correlation between stroke volume and diastolic time.

The calculated mitral valve area (Table 3) was below the normal value of 4 to 6 sq. cm.[10] in each case, the range being from 0.53 sq.cm. to 2.18 sq.cm. and it was below 1.0 sq.cm. in 8 patients.

The mean right atrial pressure (Table 4) measured at table level with the patients supine was above

TABLE 2.—BLOOD GAS AND SHUNT DATA

Blood O_2 Content in Vol. Per Cent

Case No.	O_2 Used cc./min.	Resting Arterial	Resting Venous	Arterial After Breathing 100% O_2	Arterial dO_2	Corrected O_2 Capacity	Saturation % Arterial	Saturation % Mixed Venous	L %	α %
1	207	18.6	13.4	20.6	0.26	19.2	96	69	4.0	0
2a	247	16.6	11.6	18.9	0.29	16.8	97	68	3.0	0
2b	196	17.2	11.7	19.3	0.23	18.1	94	64	6.0	0
3	231	16.6	11.0	19.4	0.18	18.4	89	59	11.0	0
4	343	16.0	8.4	17.7	0.22	16.9	93	49	5.4	2.6
5	206	21.1	13.4	22.1	0.27	21.7	96	61	1.2	9.4
6	254	15.3	8.4	18.3	0.17	17.3	88	48	12.0	0
7	290	14.5	8.3	17.9	0.17	16.5	87	50	13.0	0
8	244	14.4	10.8	15.8	0.33	14.4	98	74	2.0	0
9	227	17.9	11.6	19.3	0.27	18.4	96	63	3.6	1.6
10	234	17.3	11.6	20.0	0.23	18.1	94	64	6.0	0
11	247	17.4	10.0	20.8	0.17	19.9	87	50	12.9	1.3
12	339	19.8	13.9	21.8	0.31	20.0	97	69	3.0	0
13	219	15.0	10.0	16.0	0.26	15.4	96	64	1.7	8.9

10 mm.Hg in 5 cases. The atrial pressures were similar to the ventricular end-diastolic pressures and, except in case 2, considerably lower than the mean pulmonary capillary pressures. The ventricular and pulmonary artery systolic pressures were abnormally elevated in 9 studies, and in cases 1, 3, 8, 12, and 13 they were borderline high. In every patient, with the exception of case 2a, the pulmonary capillary mean pressure was elevated and almost as high as the pulmonary artery mean pressure in cases 1, 3, 4, 6, 12, and 13. In 2 (cases 6 and 12) of the 4 patients having clinical evidence of pulmonic insufficiency (Graham-Steell murmurs) the right ventricular diastolic pressure was equal to the diastolic pressure in the pulmonary artery. The normal right ventricular diastolic pressure observed in case 12 and the absence of clinical signs and symptoms of failure suggest that the right ventricle was well compensated.

The total resistance measured in the pulmonary vascular tree (Table 4) was elevated above a normal value[5] in all cases with the possible exceptions of cases 8 and 12. In most cases the elevated resistance was predominately at the capillary level and is a function of the valvular stenosis, although in cases 2a, 2b, 9, and 11 there was an increased pulmonary arterial resistance.

Some abnormality in pulmonary function (Table 5) was observed in all but one patient (case 13). The functional residual capacity was above the upper limit of normal (2.8 L. in this laboratory) in 5 patients, and the expiratory reserve volume was below the lower limit of normal (800 cc.) in 8 patients (case 2a, below normal while on digitalis rose to normal when studied as case 2b after stopping digitalis). In addition hyperventilation indicated by a minute breathing volume above 10 L/minute was present in 7 cases.

The maximal breathing capacity was above 100 L/minute (the lower limit of normal in this laboratory) in only 3 patients (cases 7, 12, and 13), and the ratio of breathing reserve to maximal breathing capacity was below normal (0.90 or higher) in all but cases 10 and 13.

TABLE 3.—BLOOD FLOW DATA AND MITRAL VALVE AREAS

Case No.	*Surface Area Sq. M.*	*Cardiac Rate per min.*	*Systemic Blood Flow L/min.*	*Stroke Vol. cc.*	*Diastolic Time sec.*	*Mitral Valve Area Sq. cm.*
1	1.40	75	3.98	53	0.44	1.29
2a	1.52	68	4.94	73	0.50	?
2b	1.52	77	3.56	46	0.36	0.91
3	1.66	72	4.13	57	0.53	1.23
4	2.00	71	4.52	64	0.60	0.69
5	1.54	80	2.68	34	0.34	0.60
6	1.44	80	3.68	46	0.45	0.53
7	1.78	100	4.68	47	0.42	0.57
8	1.64	105	6.8	65	0.32	2.18
9	1.73	87	3.57	41	0.42	0.62
10	1.50	72	4.11	57	0.47	0.88
11	1.69	66	3.34	51	0.53	0.63
12	1.84	94	5.75	61	0.41	1.97
13	1.68	80	4.38	55	0.33	1.89

Discussion. The present group of patients cannot be considered unselected cases of chronic rheumatic heart disease with mitral stenosis since in every case they were studied because of the possibility that they were suitable

TABLE 4.—PRESSURE DATA

Case No.	Chest A-P Depth cm	Pressure at Table Level in mm. of Hg: Rt. Atrium mean	Rt. Ventricle S/D	Pulmonary Artery S/D	Pulmonary Artery mean	Pulmonary Capillary mean	Brachial or Femoral Artery S/D	Resistance in dynes cm⁵ sec.: Pulmonary Artery	Pulmonary Capillary	Total
1	21	0	26/0	29/15	19	15	130/78	80	302	382
2a	19	7	55/7	54/27	39	4	100/60	567	66	633
2b	19	12	58/14	55/38	45	26	90/60	427	585	1012
3	20	0	31/4	29/16	18	13	115/53	97	252	349
4	26	9	47/7	47/32	35	31	120/80	71	549	620
5	17	19	58/18	49/36	43	33	107/77	298	984	1282
6	21	26	73/27	62/26	45	43	96/53	44	935	979
7	22	0	88/1	87/49	50	44	96/55	103	751	854
8	21	8	32/10	33/20	25	14	122/52	130	164	294
9	20	12	74/14	78/40	56	32	110/68	538	712	1250
10	20	8	62/9	61/28	44	25	91/76	370	486	856
11	21	9	95/12	94/44	59	29	103/63	692	718	1410
12	23	9	31/9	28/9	15	11	102/61	56	153	209
13	22	11	24/10	23/14	17	13	89/53	73	237	310

TABLE 5.—LUNG VOLUME AND VENTILATORY DATA

Case No.	Liters: Tidal Volume	Vital Capacity	Functional Residual Capacity	Expiratory Reserve Volume	Residual Volume	Total Lung Capacity	Liters/min.: Resting Minute Breathing Volume	Maximal Breathing Capacity	Breathing Reserve	Ratio of Breathing Reserve to Maximal Breathing Capacity
1	0.394	1.928	2.82	0.207	2.613	4.541	7.7	49.2	41.5	0.84
2a	0.363	2.384	2.39	0.798	1.592	3.976	7.3	51.8	44.5	0.86
2b	0.321	2.716	2.29	1.161	1.129	3.845	6.9	54.4	47.5	0.87
3	0.394	1.835	2.19	0.591	1.599	3.434	8.0	33.7	25.7	0.76
4	0.788	3.451	2.71	0.751	1.995	5.446	13.1	73.8	60.7	0.82
5	0.477	2.187	3.13	0.632	2.498	4.685	10.2	59.6	49.4	0.83
6	0.332	2.187	1.67	0.881	0.789	2.976	6.9	54.4	47.5	0.87
7	0.612	3.338	3.71	1.435	2.275	5.613	13.0	106.0	93.0	0.88
8	0.425	2.425	1.92	0.643	1.277	3.702	10.2	41.0	30.8	0.75
9	0.456	1.689	3.44	0.622	2.818	4.507	12.7	72.6	59.9	0.82
10	0.332	2.674	2.38	0.954	1.426	4.100	6.5	68.6	62.1	0.91
11	0.643	2.571	2.25	0.736	1.514	4.085	13.4	58.3	44.9	0.77
12	0.798	5.421	3.84	2.280	1.560	6.981	14.5	119.1	104.6	0.88
13	0.384	3.234	2.16	1.140	1.020	4.254	9.0	134.7	125.7	0.93

candidates for mitral valve surgery. Only those patients who were thought to have mitral stenosis as the outstanding clinical entity were studied since clinical evidence of marked aortic valve involvement or mitral insufficiency was considered contraindication to surgery. Isolated mitral stenosis was felt to be present in only 3 cases and there is anatomical validation for the clinical diagnosis in only one patient (case 7) who came to necropsy several months after this study. Mitral valvulotomy was performed in 6 of the 13 patients (cases 1, 2, 4, 5, 7, and 11) and the results of the operation will be reported separately.*

In spite of the selected nature of the patients comprising this study, a variety of valvular lesions were present and this was reflected in physiological observations of considerable individual variation, with, however, certain uniform characteristics. Although the arterial blood oxygen saturation values were not markedly abnormal, they tended to be proportional to the severity of symptoms. The deficit in complete saturation when present (cases 3, 6, 7, and 11) was the result of an increased "L" (or ventilation-diffusion) factor. In cases 5 and 13 on the other hand, there was a significant "α" factor (net right-to-left shunt) even though the arterial blood oxygen saturation was normal. Since only one of the 4 patients with an increased "L" factor (above 10%) had primary pulmonary disease (case 3 had pulmonary sarcoidosis), the increase in the other 3 (cases 6, 7, and 11) was due, most likely, to edema and thickening of the pulmonary capillaries and alveolar walls, a process which has been well described in cases of long standing mitral stenosis[30]. An extreme degree of this same pathological process could conceivably produce a shunting of blood through channels inaccessible to ventilation. Such a mechanism would give rise to an "α" factor as was found in cases 5 and 13. The plugging of a bronchus by secretions might also be the cause of an "α" shunt by making perfused alveoli inaccessible to ventilation. There was, however, no clinical evidence of excessive secretions in any of this group of patients. One of the 2 individuals exhibiting an "α" factor (case 5) had an aneurysmal dilatation of the left pulmonary artery. Both patients had had their original episode of rheumatic fever at least 20 years before the present study. The α factor in these 2 patients may have reflected the duration or the severity of their disease.

The α estimated by the Lundsgaard and Van Slyke formula and expressed as a percentage of total systemic blood flow is a "net" shunt, the resultant of the total right-to-left and the left-to-right shunts. The former shunt is due to circulation of blood through non-aerated pulmonary capillaries while the latter is a function of collateral channels between systemic and pulmonary arteries[8,15,23] or between pulmonary veins and azygos veins[28]. Bronchial to pulmonary artery collateral channels occur in conditions producing arterial anoxemia such as congenital heart disease[4] and pulmonary arterio-venous fistulas[16], and in some types of inflammatory lung disease[8,23]. Pulmonary to azygos vein channels could theoretically occur if the pressure in the pulmonary vein became greatly elevated as it does in mitral stenosis. It is conceivable, therefore, that the pathological structural changes of the lung in mitral stenosis could produce both an increased α factor, hence, arterial anoxemia, and at the same time the compensatory mechanisms, that is, col-

* The surgical procedures in these cases were performed by Dr. W. W. L. Glenn of the Department of Surgery[13].

lateral communications between vessels carrying oxygenated and those carrying non-oxygenated blood.

The mixed venous blood oxygen saturation (Table 2) was lowered more consistently than the arterial blood oxygen saturation. However, there was a significant correlation between the 2 values ($r=.71$). The relation between low venous blood oxygen saturation and heart failure is a corollary of the low systemic blood flow in the presence of a normal oxygen consumption. This relation is inherent in the equation expressing the Fick principle. The importance of the essential relationship between heart failure and a lowered venous oxygen tension has been stressed by Little[24].

In the patients studied, the rate of systemic blood flow tended to be low as might be expected in heart disease with greater venous than arterial blood oxygen deficit. The rate of blood flow was somewhat lower in the digitalized than in the non-digitalized group. This probably was a reflection of the more serious nature of the disease in the digitalized group rather than a digitalis effect since earlier studies have shown that digitalis, in the presence of heart failure usually raises the systemic blood flow[11,21,34]. This is illustrated by patient 2a who was studied while digitalized and again after digitalis had been discontinued (2b) and showed a drop in resting systemic blood flow in the later study. The patients who exhibited atrial fibrillation tended to have the lowest systemic blood flows. All of the fibrillation group (Cases 4, 5, and 6) had been digitalized. Again the lower systemic blood flows in this group probably reflect the more severe nature of their disease since they had all required digitalis and since previous studies have suggested that atrial fibrillation in the absence of organic heart disease may not affect the resting systemic blood flow[20].

Recent studies have shown a correlation between stroke volume and the period of rapid filling[19]. However, in the same studies no correlation was found between the period of rapid filling and the total diastolic time. In the present study the stroke volumes were consistently low and there was no correlation between stroke volume and diastolic filling time although the period of rapid filling, which may be correlated with the stroke volume, was not measured.

Dexter and his associates have estimated the area of the normal mitral valve orifice to be 4 to 6 sq. cm.[10]. Applying their formulae to data obtained at the time of cardiac catheterization all of the present cases were found to have markedly diminished orifices. The mitral valve areas of Cases 8, 12, and 13 were not considered small enough to warrant valvulotomy since earlier investigators, using the formulas for calculating mitral valve area, have found that above 1.5 sq. cm. the physiological effects of mitral stenosis appear insignificant[22].

In the present group of patients there appears to be an inverse proportion between the mitral valve areas and the severity of the symptoms. There is a significant correlation between mitral valve areas and mixed venous blood oxygen saturations ($r= .71$) but poor correlation between mitral valve areas and arterial oxygen saturations ($r = .20$). Since the mixed venous blood oxygen is a factor in the calculation of systemic blood flow, and the latter enters into the calculation of the mitral valve area, a correlation between the area and the mixed venous blood oxygen saturation must be interpreted with caution. There was a very high correlation between mitral valve area and systemic blood flow

(r = .73).* This, together with the difference in r values between the mitral valve area and the mixed venous blood saturation correlation on the one hand, and the mitral valve area and the arterial blood oxygen saturation correlation on the other, tends to emphasize the importance of impeded blood flow in determining the level of mixed venous blood oxygen saturation.

It should be pointed out that observations based on estimations of mitral valve area must be interpreted with caution since considerable correlation with autopsy findings will be necessary before the mitral valve area formula can be adequately evaluated. Factors such as turbulent or streaming blood flow might affect the validity of the formula and any amount of mitral regurgitation would impair the accuracy of the estimation of mitral valve area in the direction of too small a value. The recent demonstration by Ravin *et al.*[31] that all of the factors in the formula except the rate of blood flow may be replaced by empirical constants casts further doubt on the validity of the measurements. Should the determination of the mitral valve area prove to be reasonably accurate, it would still seem that a resting systemic blood flow alone would give the same information since it appears to be well correlated with the estimated size of the mitral valve[31].

A precise normal value for intra-atrial pressure cannot be stated since the exact location of the catheter tip is not known in relation to the table top which serves as the zero point for recording purposes, but right atrial pressures above 10 mm.Hg probably should be considered abnormal. By this standard, the right atrial pressure was elevated in 5 individuals, 3 of whom (Cases 2b, 9, and 13) had mild symptoms or no symptoms of valvular heart disease. In all cases the right atrial pressure tended to be similar to the right ventricular end-diastolic pressure. Although the mean pressure in the atrium is not necessarily the same as the atrial pressure at the end of ventricular diastole, the coincidence between mean atrial pressure and ventricular end-diastolic pressure in the absence of complicating factors is not surprising since the extent of atrial pressure excursions is small.

Unmistakable clinical signs of congestive failure were present in 6 patients (Cases 3, 5, 6, 7, 10, and 11), but the ventricular end-diastolic pressure was elevated in only 3. In the other 5 patients with mild signs of failure, the ventricular end-diastolic pressures were borderline or normal. Thus, in mitral valvular disease, signs and symptoms of congestive failure are not necessarily associated with right ventrical failure of a marked degree, even though radiological enlargement of the right ventricle is present.

The rise in right ventricular systolic and pulmonary artery systolic and diastolic pressures observed in most of the patients studied can be ascribed to two factors. First, a rise in pulmonary capillary mean pressure is associated with increased resistance at the capillary level. This increase in capillary resistance was uniformly present (except in Case 2a), and presumably reflects the increased resistance at a stenotic mitral valve. In addition, the pulmonary arterial resistance was also elevated in these individuals thus contributing the second factor responsible for the elevated pulmonary artery pressures. In this group of patients it is difficult to see any relation between pulmonary arterial resistance and duration or severity of symptoms. The

* When systemic blood flow is divided by surface area, the resulting index correlates even better with the mitral valve area (r=.77), and other investigators have found still higher correlations between these two functions[22,25].

small number of patients, the variation in valvular lesions present and other clinical factors probably contribute to the poor correlation between the vascular changes and the duration and severity of disease in this group.

The mean capillary pressure was increased to enormous levels in most of the patients. This no doubt produces edema of the pulmonary capillaries and alveolar walls and may account for the severe dyspnea and orthopnea experienced by many patients with mitral stenosis.

There was a significant negative correlation ($r = -.88$) between the pulmonary capillary mean pressure and the mitral valve area, the pressure being inversely related to the size of the valve orifice. This could be predicted from inspection of the formula for calculating the mitral valve area. The pulmonary capillary pressure in case 2a appears absurdly low when compared with the pulmonary artery and right atrial pressures obtained at the same time and may represent a technical error although the pressure curve appeared adequate. There may be considerable variation in pulmonary capillary pressure in different parts of the lung and the value obtained in this case may have been the result of sampling an unusually low pressure area[17]. Three months after this patient stopped taking digitalis, repeat studies revealed a mean pulmonary capillary pressure that was more in keeping with the other pressures and higher than the mean right atrial pressure.

Most of the patients had a dynamic ventilatory defect as indicated by a low maximal breathing capacity. This could be the result of poor musculoskeletal action or of diminished elasticity of the lungs. The maximal breathing capacity is, however, a nonspecific function and, while useful as a means of following the clinical course of a patient, contributes little to a knowledge of the physiological defects of mitral stenosis. Hyperventilation at rest (over 10 L/minute) occurred frequently, although it was not correlated with the complaint of dyspnea at rest. Thus the patient who complains of dyspnea is not necessarily hyperventilating. The degree of hyperventilation was neither proportional to the arterial oxygen saturation nor to the mixed venous blood oxygen saturation, indicating the likelihood that emotional factors related to the procedure influenced the minute breathing volume.*

Although the functional residual capacity was abnormally high in 5 patients (cases 1, 5, 7, 9, and 12) it was not correlated with any other physiological function measured in this study. A similar heterogeneous pattern of pulmonary function was observed in a previously reported series of cardiopulmonary disease[18].

Of probable significance was the abnormally low (less than 800 cc.) expiratory reserve volume in 8 of the 13 patients. This is consistent with the findings of other investigators in cases of congestive failure[6,7]. This finding was not correlated with other physiological or clinical findings except that 5 of the 8 patients with low expiratory reserve volumes were among the 6 patients who were on digitalis at the time of study. In an earlier report on a different group of patients the possibility was raised that digitalis indirectly alters lung elasticity which in turn might decrease expiratory reserve volume[18]. The low expiratory reserve volume in the patients of the present study who were on digitalis supports this possibility.

In the selection of patients for mitral valvulotomy the usefulness of cardiac

* In a few patients in whom serum CO_2 determinations have been made, the values have been normal. Serum CO_2 determinations have not been made in the present group.

catheterization is doubtful since the pertinent information sought from the procedure, namely the size of the mitral valve, the contour and level of the pulmonary capillary pressure curve, and the pulmonary artery resistance are in themselves of doubtful accuracy. One would hesitate, therefore, to overrule his clinical judgment as to an individual's eligibility for the operation on the authority of such inconclusive laboratory data. It is conceivable, however, that in the future a small mitral valve might in itself be a compelling indication for surgery. In such an event, cardiac catheterization, by contributing to the determination of the size of the mitral valve, might earn for itself an important place in the management of rheumatic mitral stenosis.

Summary. 1. Clinical and physiological observations obtained in a group of 13 chronic rheumatic heart disease patients with mitral stenosis and other valvular lesions are presented.

2. In each case clinical signs and symptoms were associated with a mitral valve orifice estimated to be less than one-half of the normal size.

3. The increased resistance offered to blood flow through a narrowed mitral orifice resulted in a reduction in the rate of blood flow and a general increase in pressure in the pulmonary vessels and right heart.

4. The mixed venous blood oxygen saturation was below normal in most of these cases.

5. Other phenomena observed were changes in pulmonary vascular resistance, increase in intra-pulmonary blood shunts, and a change in elasticity of the lung.

6. The significance of cardiac catheterization in selecting patients for surgical treatment of mitral stenosis is discussed.

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THE USE OF QUINIDINE IN CHRONIC AURICULAR FIBRILLATION

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During the past 25 years at least a dozen series of cases have been reported in which quinidine was used to convert patients with chronic auricular fibrillation to sinus rhythm. Various degrees of success have been described, depending upon the selection of cases, the dosage and method of quinidine administration and the concomitant use of other drugs such as digitalis. Most authors have reported very good results, dating from the early papers of Maynard[6], and Parkinson and Campbell[8] up to the very recent reports of Yount, Rosenblum and McMillan[13], Holzman and Brown[4], and Goldman[2]. In spite of this, interest in the problem of converting the chronic fibrillator seems to wax and wane, possibly due to occasional reports of untoward reactions and sudden death occurring while on quinidine, and an unwarranted belief that embolization will frequently ensue when sinus rhythm is restored. It is the purpose of this paper to present the results obtained in 34 cases of chronic auricular fibrillation treated with quinidine in an attempt to restore and maintain sinus rhythm. The cases were collected over an 18-month period from the medical service of St. Catherine's Hospital, Brooklyn.

Material. Thirty-four patients with chronic auricular fibrillation were chosen because of the presence of one or more indications which will be discussed later. The exact period of fibrillation in many cases was not definitely known, but all were known to have been fibrillating not less than several weeks, most for at least several months, and some for one to two years. Nine patients had a definite history, and others a strongly suggestive history of one or more episodes of embolization, either systemic or pulmonary. Etiologically the group was mixed, consisting of 13 cases with arteriosclerotic heart disease, 14 with rheumatic heart disease, 4 with hypertensive and 3 with thyroid heart disease. The predominating valve lesion in the rheumatics was mitral stenosis with some cases showing various lesser degrees of mitral insufficiency. None showed clinical evidence of rheumatic activity. The 3 thyroid patients had received adequate therapy to abolish signs of thyrotoxicosis and bring the BMR within normal limits; 2 with propyl-thiouracil and Lugol's solution, one with thyroidectomy. The average age for the entire group was 58 years; the youngest being 24, the oldest 80 years. The average age in the arteriosclerotic and the rheumatic groups, which were the largest, differed considerably as might be expected. In the arteriosclerotic group the average age was 64; in the rheumatic group, 51 years. All of the patients in the series had appreciable cardiac enlargement, which, if graded I to IV, would fall mostly in grades II and III, with 2 cases in grade IV. More than half of the patients had been in congestive failure one or more times.

Procedure. Whenever possible the patients were digitalized and regulated on the proper maintenance dose for a brief period prior to the use of quinidine. Since all patients in this series suffered from a rather serious degree of heart disease, most had been receiving digitalis as a part of their routine cardiac therapy. Those who had previously presented no particular need for digitalis were nevertheless digitalized prior to attempted conversion with quinidine. The history of recent digitalis intoxication, due to hypersensitivity to the drug, however, precluded its use in a few cases.

Electrocardiograms were taken prior to the first dose of quinidine and prior to any increment in the dose. Additional tracings were taken if any unusual change in rate or rhythm occurred. Provided no contraindication existed the following schedule was carried out. After a dose of 0.2 gm. to test for idiosyncrasy to quinidine, 0.2 gm. was administered every 2 hours for 6 doses. Blood pressure, pulse and general condition of the patient were noted between doses.

If the patient did not revert to sinus rhythm on that dosage, no further quinidine was given until the following day, since it was felt that proper observation of the patient throughout the night was difficult and that it would be unwise to repeatedly deprive cardiacs of this type of their night's sleep. Each subsequent day the individual dose was increased by 0.2 gm., up to the point where conversion occurred, or the dosage of 0.8 gm. every 2 hours was reached. If fibrillation continued after this dosage no further attempt at conversion was made. The above schedule of administering the drug every 2 hours with daily increments was chosen for the following reason. Sokolow[11], in his experimental work with quinidine, has shown that after several doses of any given amount of quinidine at one to two-hour intervals, a certain blood-level is obtained, which cannot be elevated by repeated doses, but rather the amount of the individual dose must be increased. It was soon observed, in our series, that quinidine in large doses is better tolerated if begun in the afternoon after breakfast and lunch had been eaten. For this reason, in the latter part of the series, medication was given during the 12 hours between noon and midnight and fewer gastrointestinal upsets resulted. If slight to moderate nausea or diarrhea occurred it could be controlled, for the most part, by the use of Amphogel or paregoric. A moderate degree of bradycardia or tachycardia occurred in a few cases which, however, did not necessitate discontinuing the drug. When conversion to sinus rhythm was suspected clinically, it was confirmed by an electrocardiogram, since a regular 2:1 or 3:1 flutter can be confused, at the bedside, with sinus rhythm. The patient was then placed on quinidine 0.2 gm., 4 times a day as a maintenance dose.

Results. Of the total group of 34 patients, 24 were converted to regular sinus rhythm for an over-all result of 70.6% successful conversion. The degree of success, however, varied considerably in the different etiological groups. All 3 thyroid cases were converted, having previously been restored to the euthyroid state by specific therapy. Twelve of the 13 arteriosclerotics were restored to sinus rhythm. In the rheumatic group 7 of the 14, or 50%, were converted. In the small hypertensive group, 2 out of 4 were converted for a similar result of 50%.

In reference to the dosage required to effect conversion, 13 in the series were converted on the day they were receiving 0.4 gm.; 8 while on 0.2 gm.; 3 while on 0.6 gm. There was no case converted on 0.8 gm. Six of the 8 converted on 0.2 gm. were from the arteriosclerotic group. Reactions severe enough to require discontinuing the drug were observed in 6 cases. In addition, one patient died the day after apparent conversion to sinus rhythm. She was a 58-year old rheumatic with severe mitral stenosis and a very recent hemiplegia from embolization. After having received the 0.4 gm. dosage she was observed at the end of the day, to have sinus rhythm and to be resting comfortably. The following morning she died in her sleep. The necropsy revealed active rheumatic heart disease, severe mitral stenosis and a ball-valve type of thrombus in the left auricle. No evidence of a peripheral embolus was found. The reasons for discontinuing the drug in the 6 cases in which this was necessary are as follows: Three exhibited diarrhea or vomiting. One patient with hypertensive heart disease developed complete heart block during the second day of quinidine therapy. The drug was stopped and within 24 hours the heart block had disappeared and the rhythm had returned to auricular fibrillation. Another, a 63-year-old rheumatic with severe mitral stenosis and marked cardiomegaly, had been in irreversible congestive failure for many months, with an associated hydrothorax. Following the second 0.2 gm. dose of quinidine she developed a very rapid, regular rhythm, which proved on the electrocardiogram to be flutter. This was followed by a shock-like state and acute pulmonary edema. After intense emergency measures the patient

recovered. The next day she reverted to auricular fibrillation and her general condition was the same as before quinidine therapy. Another rheumatic, aged 55, developed a fixed flutter. No untoward reactions were observed from the maintenance dosage of quinidine.

A follow-up was possible on 22 of the 24 patients converted. Two patients reverted to auricular fibrillation within a week after conversion and although sinus rhythm was again restored, it could not be maintained. Three others, who had been converted, died during the 18-month follow-up period; 2 as a result of congestive failure; one due to causes unknown to us. Of the remaining 17, 16 have maintained sinus rhythm. The period of time for each varies, from 18 months, in the case of the first patient in the series, to 3 weeks in the case of the patient most recently converted. Three have been observed to be in sinus rhythm for one year. Thus, of the 22 converted patients, whom we were able to follow up, 19 are living; and of the 19, 16 have maintained sinus rhythm.

Discussion. The question naturally arises whether restoring sinus rhythm is of definite advantage to the patient, and if so, under what circumstances. In cases of recent fibrillation, that is, when it has existed for only a period of a few hours up to a few days, there would be little hesitation in the minds of most in attempting to restore sinus rhythm. The problem of the chronic fibrillator, however, has always been considered more complex. In this series the indications for attempting conversion were the following:

(1) History of single or multiple episodes of embolization.
(2) Persistent congestive heart failure, in spite of the usual regimen for decompensation.
(3) Diminished cardiac reserve, just short of heart failure, which makes the patient practically an invalid.
(4) Anxiety and distress on the part of the patient resulting from an awareness of the irregular cardiac impulse.

In reference to the first indication, the catastrophic results of single, and even more so, of repeated emboli to the lung or peripheral arteries is common knowledge. The frequency of emboli as the cause of death in rheumatic heart disease has been shown by Laws and Levine[5] to be greater in the ratio of seventeen to one in chronic fibrillators compared to patients with sinus rhythm. It would certainly seem that some active treatment or prophylaxis should be attempted in these cases rather than sit by and assume the role of a silent observer of these embolic phenomena. In reference to the second and third indications concerning cardiac efficiency, Dressler[1] summarized the situation when he empirically stated that "the absence of proper auricular action necessarily reduces the efficiency of ventricular contraction." In reviewing the literature one finds that experimental results differ as to the degree of increased efficiency achieved by the restoration of sinus rhythm, depending upon the methods of study employed. Very recently, however, Hansen[3] and his associates have reported on the favorable changes in hemodynamics brought about by the restoration of sinus rhythm in patients who were chronic fibrillators. The studies were carried out by means of cardiac catheterization, which revealed a significant rise in cardiac output and a decrease in pulmonary blood volume in the majority of patients after sinus rhythm was restored by the use of quinidine. Phillips and Levine[9] have shown that auricular fibrillation, *per se*, produces cardiac dilatation and progressive heart failure in patients with otherwise normal hearts. In the case

of the cardiac who is responding poorly to the usual regimen for congestive failure, conversion to sinus rhythm may afford just that margin of benefit necessary to produce a satisfactory response. In reference to the fourth indication, it is readily admitted that in some individuals, fibrillation causes little or no discomfort. In many other individuals, particularly those with a thin chest wall or a chest of small anterior-posterior diameter, considerable awareness of the arrhythmia exists, producing a state of mind wherein they are always heart-conscious and are prone to develop a cardiac neurosis in addition to their organic disease. These patients are usually bothered most either when at complete rest or following exertion or emotional upset.

It was felt that some patients presented too great an inherent risk for quinidine therapy because of the presence of active subacute bacterial endocarditis, frank rheumatic activity or conduction defects such as bundle-branch block and complete heart block. These were considered contraindications to quinidine therapy.

Regarding the degree of success to be expected, the etiology of the fibrillation would appear to be an important factor. The highest degree of success was in the thyroid group, namely, 100%; however, the group was small, consisting of only 3 patients. The arteriosclerotic group was next highest with 12 of 13 cases being converted, for a result of 92%. Of the 14 rheumatics and 4 hypertensives, 50% of each were converted. This is in contrast to the results of McMillan[7] and Welfare and Saland and Frank[10] who had greater success with rheumatics than with arteriosclerotics. Yount[13] *et al.* found the degree of success about equal in the 2 groups. The duration of fibrillation did not affect the likelihood of conversion and the maintenance of sinus rhythm since the first case in the series, 18 months ago, and several others early in the series, were among the most chronic of the fibrillators and were nevertheless converted and are still in sinus rhythm at the present time. The quinidine dosage on which the greatest number converted was 0.4 gm. every two hours. Beyond the dosage of 0.6 gm. every 2 hours none was converted. In several cases near the end of the series, 0.4 gm. was repeated for 2 days rather than increase the dose, since this was found to be such a favorable dosage. Occasionally a dose was given hypodermically to tide the patient over when nausea was prominent. There was little difference in the age group of those who converted and those who did not, and there was a fairly even distribution of the ages in each group. It was also noted that less quinidine was needed to bring about conversion in the arteriosclerotic than in the rheumatic group.

Flutter was observed frequently in this series. Five of the 24 cases converted and 4 of the cases not converted showed auricular flutter at some time during quinidine administration. Goldman[2] also reports a high incidence of flutter in the course of administering quinidine to patients with auricular fibrillation. Since flutter is so commonly observed as an intermediary stage between auricular fibrillation and sinus rhythm, it is perhaps alway an intermediary mechanism during conversion, but not always observed because of its brief duration. In view of this, the importance of digitalizing the patient prior to giving quinidine is clear, namely, to protect the ventricle against the onset of a very rapid rate which is prone to occur in auricular flutter, particularly when a low degree of block is present, such as 1:1 or a 2:1 block. This would seem to be of special importance in a group of patients with severe organic lesions. Where

flutter did not occur there was very frequently a change in the type of fibrillation, as seen on the electrocardiogram, from a fine to a coarse type, with large clear "f" waves occurring at a more regular rate. A prolongation of the P-R interval, or first degree heart block was present in several cases when sinus rhythm appeared. This usually disappeared when quinidine was reduced to the maintenance dose. Except for the one case of complete heart block mentioned above there was no appreciable change in the QRS complex during or after therapy.

Conclusions. An attempt should be made to convert patients with chronic auricular fibrillation to regular sinus rhythm if proper indications exist, since conversion to, and maintenance of regular sinus rhythm is possible in a large percentage of cases, with little risk, and with great improvement in the patient's well-being. Those whose fibrillation is due to arteriosclerotic heart disease showed the best results in this series. A certain inherent risk exists in the treatment of patients with heart disease, but during the course of quinidine therapy there is no appreciable increase in the risk of embolization or sudden death in chronic fibrillators over and above that which already exists as a result of the disorder itself. This has been shown to be true in the works of Viko and White[12], Parkinson and Campbell[8] and several other authors in careful statistical studies. If the contraindications are looked for and recognized, any risk involved in the therapy is lessened. The one instance of sudden shock and pulmonary edema associated with rapid auricular flutter occurred in a 63-year old rheumatic who unquestionably had the least cardiac reserve and the greatest degree of cardiomegaly in the entire group. Probably the risk in such cases is out of proportion with the benefit to be derived.

What untoward reactions occurred did so on doses of 0.4 gm., or less, hence reactions are not to be expected in greater frequency with increasing doses. No patient who received the dose of 0.8 gm. showed any toxic reaction. Comparing the etiological groups it can be said that the arteriosclerotics converted on smaller doses than the rheumatics.

The follow-up of these cases indicates that sinus rhythm can be maintained in a large percentage of those converted and that it is insured by a small maintenance dose of quinidine. Further follow-up of these cases reported as well as newer cases being converted will be carried out in the future. In order to properly evaluate quinidine therapy, the problem must be approached statistically, since not only the possibility but also the frequency of complications must be weighed against the benefits to be obtained.

Summary. 1. Twenty-four out of 34 patients with chronic auricular fibrillation were converted to regular sinus rhythm with quinidine.

2. Patients with arteriosclerotic heart disease and thyroid heart disease showed the best results.

3. The dosage schedule of quinidine is practical and based on knowledge of the behavior of quinidine blood-levels.

4. Digitalis is indicated as a preparatory measure to afford protection against a very rapid ventricular rate.

5. A large percentage of those converted have maintained sinus rhythm for periods ranging up to 18 months.

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WEIGHT REDUCTION: A STUDY OF THE GROUP METHOD: PRELIMINARY REPORT

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Realizing the need for a way of reducing a large number of people efficiently and economically, and recognizing the successful use of group methods in certain other fields, we undertook a study at this hospital in the fall of 1950 to determine the effectiveness of a group approach to the problem of weight reduction. The study was made possible by a grant from the California State Department of Public Health through its Bureau of Chronic Diseases.

Procedure. In the first year, a frankly exploratory period, a group of 107 overweight volunteers (100 women, 7 men) were secured and, after physical examinations and laboratory tests, were assigned to groups which met with professional leaders. These groups were formed arbitrarily as people completed the examination procedures and in whatever numbers the leader chose to work with. Eight groups, therefore, varied in size from 8 to 28 members.

Leaders, selected on the basis of interest and experience in group work, were 2 nutritionists, a psychologist, a physician, an instructor in social group work, a health educator, and an instructor in adult education assisted by 3 graduate students. There was no rigid plan for leadership, each leader being encouraged to use his own methods in attempting to achieve weight loss in the group. In three of the groups a reduction diet was given at the outset as an authority act, in three others the diet was withheld until discussion led to a group decision to go on a diet, and in two groups a request for a diet to follow was left to individual initiative. With the exception of one group which met on a bi-weekly schedule, all groups met once a week over varying periods of time from 3 to 7 months, totaling in number from 13 to 23 meetings.

Results. In the variously led groups there was no great difference in the amounts of individual weight loss. Attendance varied considerably among the groups and hence there were differences in the total weight lost by the groups. There were 79 participants who attended a quarter or more of the meetings held for their respective groups; those attending fewer than this were considered to have dropped out of the project, since their weight records were so incomplete. Forty-one participants lost 10 or more pounds; of these, 20 lost 20 or more pounds. The maximum individual weight loss was 43 pounds. Five neither lost nor gained and 17 gained 1 to 8 pounds; 1 gained more than 20 pounds. The total weight lost by the 79 participants was 901 pounds.

Further Procedure. The results were considered encouraging enough to warrant further study and to suggest that the group method is effective. The project was continued therefore into a second year. On the basis of the experience gained the first year the plan was modified in several important respects:

1) Each applicant was carefully oriented as to the procedures to be expected during the course of the study (namely, initial physical examination, laboratory tests, nutrition interview, psychological tests, and repetition of these for comparison). In addition, the responsibility of each participant for regular attendance at 16 weekly meetings, for adherence to the prescribed diet, and for availability for follow-up was emphasized.
2) For control of methodology, the 109 participants, all women, were divided at ran-

dom into two groups which were to be exposed to two different approaches. These groups were then divided into those above and those below age 40 and gathered together for homogeneity into eight groups composed of about 14 members each.

3) In an attempt to contrast a direct "nutritionally-centered" as opposed to an indirect "psychologically-centered" approach, the group leaders were selected and oriented to reflect this difference, namely: the former groups were led by a health educator and a nutritionist, the latter by an instructor of social group work and a psychiatric social worker. Each leader had both an "older" and a "younger" group.
4) As an expected discipline for participation, every individual in each group was furnished an identical diet, the composition of which was essentially 1000 calories with protein 80 gm., carbohydrate 80 gm. and fat 40 gm.

Results. At the conclusion of the 16-week period there remained 93 of the original 109 participants who had attended more than 4 meetings. Seventy-seven lost 10 or more pounds; of these, 46 lost 20 or more pounds. The maximum individual weight loss was 51 pounds. Only one did not lose; none gained. Of the remaining 15 who lost 1 to 10 pounds, 11 lost more than 5 pounds. The total weight lost by the 93 was 1730 pounds. There was no appreciable difference in the records of weight loss as between the two types of groups.

The blood pressure, cholesterol level and macromolecule (Sf 10-20 and Sf 20-100) concentrations were checked repeatedly. It is expected that studies of these data will be available in the future.* Those electrocardiograms initially abnormal were repeated. It is interesting to note that an appreciable fall in blood pressure was observed in each individual with initially elevated pressure who lost weight.

At this point in our study we have been able to contact 74 of the first group at the end of one year. Of these, 38 had lost 10 or more pounds during their active participation in groups. Of the 38, 10 stated they have continued to lose 1 to 21 pounds; 3 stated they have maintained their weight; and 25 stated they have gained 1 to 28 pounds. Seventeen who had not lost a significant amount of weight (that is, less than 10 pounds) during the project, reported that they have since lost from 2 to 40 pounds.

It would appear from the total experience reported above that a group approach to weight reduction is effective. If, however, the scope of the investigation includes also, as it should, the applicability of the group method to community projects, then this conclusion is not warranted until adequate follow-up study of five or more years demonstrates significant achievement and maintenance of ideal weight goals for the majority of participants.

In such studies as this, purely objective findings are necessarily few, impressions are many. These, too, deserve discussion.

The etiology of obesity has been variously described as hereditary, familial, environmental, endocrine, pathologic, or psychologic. Many investigators consider obesity to be due to overeating, itself a symptom of emotional disturbance. That this is true is not doubted. It is felt, however, that in a significant number, the obesity, whether psychological factors exist or not, is a product of any one or a combination of such other factors as geography, familial eating habits, cultural folkways, economic situation, or ignorance. In this connection it is interesting to note that the psychologically-oriented groups were as concerned about their diet as those nutritionally-oriented were in discussing their emotional problems.

* Dr. John Gofman and Associates, Donner Laboratory, University of California, Berkeley, California.

The outstanding characteristic of a group of individuals is that they react interpersonally; in so doing, self-therapy is promoted. The group itself may, therefore, provide its members with sufficient opportunity for self-understanding without the need for professional psychological interpretation. And, except for research purposes, perhaps anyone, provided he is "people-minded" and sympathetic to the problem and is assisted by instruction or advised by manual or consultation, can successfully work with a group to the end that weight is lost. Since ignorance of dietary needs cannot be pooled by group members to provide intelligent guidance for themselves, such information must be authoritatively provided.

The striking improvement in total and individual weight loss the second year we believe due primarily to: 1) careful and detailed orientation of the individual at the outset, and 2) the relative homogeneity of the groups. Without specific objective data, and judging only by the facts of improved attendance and better weight loss, we feel that the groups in such a project should be carefully constituted, so that they contain individuals of the same sex and approximate age range. Perhaps grouping by like socio-economic or educational level, and degree of overweight may have additional advantages.

It is our impression that psychological screening tests are of importance not only in gaining insight into the personality of the obese but also, perhaps, as an instrument for forming workably homogeneous groups by eliminating psychotic or intractable individuals from participation in the groups. Further, we are exploring the use, to be reported later, of such a battery of tests as a screening device by which probably-successful response to a group situation might be recognized in advance. This could make possible, for example, the differentiation of those who would meet their goals in a short-term didactic course from those who would respond to such simple group work as has been outlined above, and finally from those who require intensive psychotherapy over a longer period.

For testing purposes a program of 16 weeks' duration proved to be adequate. In community application probably no such arbitrary schedule should be adopted. Those who have most to lose need longer supervision.

Conclusions and Impressions. 1) The group approach to weight reduction here described is effective in bringing about satisfactory weight loss for a majority of participants.

2) Long-term follow-up is believed necessary to demonstrate whether there will be a significant achievement and maintenance of ideal weight goals, in order to determine the ultimate effectiveness of group methods for community projects.

3) The group itself appears to satisfy, at least in part, whatever need may exist for psychotherapy in most overweight individuals.

In the second year of the project, use was made of carefully devised pre- and post-participation nutrition interviews, psychological tests, and repeated statement of post-meeting reactions, as well as physical examinations and laboratory tests. A mass of material thus has been accumulated of special interest in the fields of nutrition, social group work, and psychology which it is expected will be reported in detail as the data become available.

A PYROGEN-LIKE COMPLICATION OF CARDIAC CATHETERIZATION: ITS PATHOGENESIS

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In the course of cardiac catheterizations performed at this hospital late in 1951 and early in 1952, reactions, characterized by chills, fever, prostration, headache and backache, occurred in 9 patients who had mitral stenosis, either alone or complicated by mitral insufficiency.

At the time these reactions were observed, we were unaware that others also were encountering the same complication. This became apparent when the reports of Houssay, Haynes and Dexter[3], and of Miller and co-workers[4] appeared. These investigators found localized lung lesions on roentgenography of their patients, and considered the complication to be pulmonary infarction. We did not take roentgenograms of our patients following these reactions, but felt that another explanation was more likely, as suggested by the work of Dameshek and Neber[2]. They reported similar reactions following compatible whole blood transfusions, which they attributed to a heat-labile plasma fraction. This fraction, later called "PTR" factor by Crosby and Stefanini[1], could be removed from red blood cells by repeated washings.

We found that, when we washed our catheters repeatedly with saline, reactions no longer occurred. We therefore believe that a factor similar to, or identical with, the "PTR" factor is responsible for the pyrogen-like complication following cardiac catheterization.

Material and Methods. Eighty-four patients, suspected or known to have some form of heart disease, were subjected to right heart catheterization, according to standard technique[6]. Of these, 57 had congenital defects; 24 had rheumatic heart disease with mitral stenosis, either alone or complicated by mitral insufficiency; 2 were normal; and 1 had a peripheral arteriovenous fistula. In each case, an attempt was made, under fluoroscopic visualization, to pass the catheter as far as possible out into the pulmonary periphery in order to record the "pulmonary venous capillary" ("PVC") pressure. Criteria for rheumatic and congenital heart disease were those of the American Heart Association[5].

Early in our studies, we handled our catheters* as follows:

Upon withdrawal from the patient, the catheter was flushed once with 50 cc. of sterile physiologic saline or tap water, and then dried. Although an effort was made to do this immediately after the catheter was withdrawn from the patient, occasionally 15 or more minutes elapsed. Prior to re-use, the catheter was sterilized for 30 minutes in a columnar tube filled with Detergicide* (1:667 dilution, prepared by adding 15 cc. of the concentrate to a gallon of tap water). Then the catheter was rinsed in a pan of sterile physiologic saline and flushed through the inside several times with 50 cc. of saline.

When we observed the unusual complications reported here, we modified our technique in an effort to eliminate them. Besides using extra sterilization precautions, we changed all our rubber tubing. This did not prevent further reactions, so we replaced all

* Manufactured by United States Catheter & Instrument Corp., Glens Falls, N. Y.

the rubber tubing with plastic tubing. This also was ineffectual. We then substituted a continuous drip for the pressure bottle used to flush the catheters. As this still failed to curb the reactions, we completely altered our technique of handling the catheters as follows:

Instead of just a single washing and flushing of the catheter after use, it was now repeatedly washed and flushed with sterile saline. It was then hung at full length for at least 30 minutes in a columnar tube containing Detergicide, the fluid being drawn through the lumen of the catheter several times by syringe. Then the catheter was flushed for an hour with running tap water under pressure, dried by suction for 30 minutes, and stored in a covered glass container. Prior to use, the catheter was resuspended in Detergicide for 30 minutes, washed and flushed in three successive basins of sterile saline, and finally flushed with 50 cc. of saline from a drip bottle.

Results. Since this procedure was instituted, we have not encountered any further reactions following cardiac catheterization.

The 84 patients can be divided into two groups: Group I, catheterized before February 26, 1952, with the original technique; and Group II, catheterized thereafter with the modified procedure.

Group I consisted of 32 patients, of whom 20 had congenital heart disease, 11 had rheumatic heart disease, and 1 had a traumatic peripheral arteriovenous fistula. Nine of the 11 patients with rheumatic mitral stenosis had reactions characterized by chills, fever (101° to 103.4° F.), prostration, headache and backache. The symptoms terminated in one day in all cases, except one in which they lasted two days. In this patient, in addition to the other symptoms, chest pain, cyanosis and ST depression in the electrocardiogram were present.

No untoward effects occurred in the congenital heart disease cases and the one case of arteriovenous fistula, although "PVC" pressures were taken in practically all of them. The reactions were observed only in cases of mitral stenosis.

There was no direct correlation between the extent of probing in the pulmonary capillary area and the severity of the reaction. The most severe reaction occurred in a case in which the catheter did not even reach the pulmonary artery.

Group II included 52 patients, of whom 37 had congenital heart disease, 13 had rheumatic heart disease, and 2 were normal. In none was there any untoward reaction whatsoever following cardiac catheterization. All were studied using catheters which had been sterilized and treated by our new procedure. One of the mitral stenosis cases was in congestive heart failure and had a "PVC" pressure of 35/23 mm. Hg, but still had no reaction.

Discussion. There is a striking similarity in the clinical picture of the complications observed in our patients following cardiac catheterization and those reported as pulmonary infarctions by Houssay, Haynes and Dexter[3], and by Miller and associates[4]. These reactions were so disturbing that, like Houssay, Haynes and Dexter[3], we were seriously considering discontinuing catheterization in cases of mitral stenosis. However, in view of the importance of the procedure as an aid in evaluating such cases for mitral commissurotomy, we made every effort to eliminate them. In doing so, we considered three possible explanations of their pathogenesis.

1. BACTERIAL INFECTION. The possibility of a pathogenic bacterium being introduced by means of the catheter was eliminated, because of the promptness with which each reaction subsided and because no reactions occurred in cases of congenital heart disease catheterized during the same period with the same group of catheters.

2. TRAUMA. If such reactions were due to jamming the catheter into the small arteriolar radicals, then heating or washing would not be expected to have any effect. The fact, that one of our patients, in whom the catheter was not advanced into the pulmonary arteriolar region, still had a reaction, further supports our contention that trauma does not play a significant role in this complication.

3. PYROGEN-LIKE REACTION. The clinical picture in our catheterization complications could be logically explained as a pyrogen-like reaction to a factor similar to, or identical with, that described by Dameshek and Neber[2], as responsible for pyrogen-like reactions occurring during compatible whole blood transfusions. Even the roentgenologic changes, localized rales and hemoptysis reported by Miller[4], and the syndrome reported by Houssay[3] (chills, fever, prostration, headache and backache), could be explained on the same basis. These authors, however, felt the reactions were thrombotic in origin, since all roentgenologic and auscultatory changes were confined to the area of farthest penetration of the catheter tip. We feel that small emboli to the lungs might account for their findings. Such emboli were suggested by Crosby and Stefanini[1], when they found increased blood coagulability during "PTR" (plasma transfusion reactions).

Plasma transfusion reactions could be prevented by removing the "PTR" factor with heat or repeated washings with saline. Similarly, the catheterization complication was eliminated by Houssay, Haynes and Dexter[3] by autoclaving the catheters, and by us by repeatedly washing the catheters in saline. We prefer washing to heating, because heat damages the catheters.

If the reactions following cardiac catheterization are due to a pyrogen-like factor, such as the "PTR" factor, then it is logical to have expected them to occur in both the congenital and mitral stenosis cases. Their absence in the congenital cases, both in our experience and in that of others[3,4], raises the question: why are the reactions limited to rheumatic mitral stenosis? There are two possible explanations:

First, the pathologic changes in the pulmonary epithelium of patients suffering from rheumatic mitral stenosis may render this tissue more susceptible to the "PTR" factor.

Second, there may be certain conditions in which there is a predilection to plasma transfusion reactions. This is suggested by the fact that 10 of the 11 cases of plasma transfusion reactions reported by Dameshek and Neber[2], and the 3 cases described by Crosby and Stefanini[1] were suffering from some form of blood dyscrasia. It is possible that rheumatic fever, in which hypersensitivity plays a prominent role[7], is attended also by some hematologic alterations, which result in increased sensitivity to the "PTR" or "PTR"-like factor. When this factor is introduced into the blood stream of patients with mitral stenosis by means of inadequately washed, used catheters, a reaction similar to the plasma transfusion reaction occurs. Congenital heart disease patients, on the other hand, do not respond adversely, indicating that they may lack this "PTR"-sensitivity.

Summary. 1. A pyrogen-like syndrome, characterized by chills, fever, prostration, headache and backache, was observed following cardiac catheterization in 9 of 11 patients with mitral stenosis.

2. These reactions were eliminated by subjecting the catheters to thorough washing with saline. Heat also has been found effective[3].

3. It is believed that these reactions are similar to pyrogen-like reactions

reported by Dameshek and Neber[2] following transfusions of compatible whole blood. A factor similar to, or identical with, the heat-labile "PTR" factor described by these investigators and by Crosby and Stefanini[1] may be responsible for the cardiac catheterization complication.

4. Two possible explanations are given for the occurrence of the complication only in mitral stenosis and not in congenital heart disease.

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HEMOLYTIC TRANSFUSION REACTION CAUSED BY ANTI-c ANTIBODY

(With a note on the application of the Coombs test to crossmatching procedures)

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The increasing use of blood transfusions as an important therapeutic adjunct in medicine has been accompanied by increasing risks of sensitization and hemolytic reactions to antigens of relatively low sensitizing capacity. This is a report of a hemolytic transfusion reaction resulting from the administration of blood containing the antigen c (hr') to a recipient possessing a specific antibody for this antigen. A new crossmatching program has been instituted, utilizing the Coombs test, in an attempt to detect such incompatibilities and prevent reactions.

Case Report. The patient was a 43-year-old housewife who has been followed at the University of Minnesota Hospital since 1930. Except for scarlatina and typhoid fever as a child, the patient has always been in excellent health until 1947, when she noticed progressive enlargement of her neck. On admission to the hospital (June 13, 1952) the thyroid gland appeared diffusely enlarged, but there were no symptoms or signs of either hyperthyroidism or myxedema. The rest of the physical examination was essentially negative.

Laboratory data included a negative urinalysis. The hemoglobin was 13.7 gm. %. Leukocytes numbered 3700/c. mm. with a normal differential count. The serum cholesterol was 183 mg. per 100 cc. A glucose tolerance test curve was normal. The basal metabolic rate was +8%. Radioactive iodine (I_{131}) uptake was 22% in 24 hours. The protein bound I_{131} was 33% in 24 hours. The Wassermann test on the blood serum was negative.

The patient underwent an elective subtotal thyroidectomy on June 18, 1952. During surgery she received 2 units of 500 cc. of citrated blood. The surgical procedure was technically quite difficult and lasted 4½ hours. Immediately after starting the first bottle of blood there was a marked rise in systolic blood pressure from 140 mm. Hg. to approximately 210 mm. Hg which lasted for one hour. The diastolic pressure remained stable around 80 mm. Hg. The second bottle of blood had no effect on any vital signs. No unusual bleeding was noted. After transfer to the surgical recovery room the patient's pulse rose to 140, the temperature was 102.8° F., and the respiratory rate to 28. It was first thought that the patient had a postoperative thyroid storm, but the lack of preoperative metabolic abnormality militated against it. The urine specimen collected in the recovery room was mahogany brown in color, and gave the clue to the diagnosis of a hemolytic transfusion reaction. The plasma hemoglobin level at that time was 206 mg. per 100 cc. The postoperative course was rather prolonged because of a temporary episode of uremia, but the patient recovered completely. The blood urea nitrogen rose to 96 mg. per 100 cc. on the 6th day and returned to normal on the 44th day after the reaction.

History of Pregnancies and Previous Transfusions. The patient had had 13 pregnancies (Table 1). Three of them (3rd, 4th, 5th pregnancy) resulted in spontaneous abortions and one was a stillbirth (12th pregnancy). The gross necropsy and the histological studies of the stillborn infant and the placenta did not reveal any changes suggestive of erythroblastosis. The cause of death could not be determined. None of the living children had any clinical evidence of erythroblastosis after birth and the routine postpartum blood smear studies of the last 3 children did not show any increased number of normoblasts.

In 1932, the patient was given a direct transfusion of uncitrated blood because of anemia following her third abortion. She received 360 cc. in 30 minutes and reacted with a severe chill and an acute backache.

Determination of the Type of Antibody. It can be seen from the data

in Tables 1 and 2 that the patient could have been sensitized to 3 types of antigens: A_2, c, and d. The presence of an anti-d antibody in her serum was considered extremely unlikely, since there are only 2 reported instances in the literature[6]. For the detection of an anti-c or anti-A_2 antibody the patient's serum was tested against a panel of selected erythrocytes containing the antigens A_2 and c (Table 3). The positive reaction in test 1 could be caused by either anti-c or anti-A_2 antibodies. The negative test 2 excludes the anti-A_2 antibody and the positive test 3 is definite evidence for the presence of an anti-c antibody. No other types of antibodies could be detected.*

Both bottles of blood given during surgery contained the antigen c and the first one only probably accounted for the sudden hemolytic episode.

The mechanism of sensitization is obvious from the study of the family members (Table 1). The patient's husband is heterozygous in respect to the gene C/c. The chromosome cde has been transmitted to 6 of the living children. Because of the lack of data regarding the pregnancies which resulted in abortions or stillbirth, it is impossible to state the exact number of pregnancies which might have had a sensitizing effect on the mother. The blood donor of 1932 was recently typed with Rh sera and found to be homozygous for the gene c. There is good historical evidence that the patient suffered a hemolytic transfusion reaction in 1932 which suggests that she was already sensitized at that time. In conclusion, it is possible to state that the patient acquired the anti-c antibody during a total of 6 pregnancies

TABLE 1.—HISTORY OF PREGNANCIES WITH REFERENCE TO THE GENOTYPE OF EACH FAMILY MEMBER

Family Member	*Date of Birth*	*Genotype*
Patient	Sept. 27, 1908	A_1B CDe/CDe MN
Husband	May 28, 1906	A_2O CDe/cde MN
Daughter P.	Sept. 18, 1926	B O CDe/CDe
Son C.	July 30, 1928	A_1O CDe/cde
Abortion (2nd month)	Feb. 9, 1930	
Abortion (3rd month)	June 24, 1930	
Abortion (2nd month)	May 28, 1932	
Daughter L.	Oct. 4, 1933	B O CDe/cde
Daughter R.	Dec. 27, 1934	A_1O CDe/cde
Son G.	July 5, 1937	A_1O CDe/CDe
Son R.	Oct. 20, 1938	A_2B CDe/CDe
Son W.	Aug. 24, 1947	A_1O CDe/cde
Son T.	April 2, 1949	A_1O CDe/cde
Stillbirth	Jan. 25, 1951	
Son Rb.	April 20, 1952	B O CDe/cde

TABLE 2.—HISTORY OF TRANSFUSIONS

Date	*Volume*	*Type*	*Reaction*
July 5, 1932	360 cc.	A, cde/cde	Chill and backache
June 18, 1952	500 cc.	A_2B cde/cde	Hemolytic reaction
	500 cc.	A_2B CDe/cde	

In conclusion, it is possible to state that the patient acquired the anti-c antibody during a total of 6 pregnancies

* Dr. P. Levine of the Ortho Laboratories in Raritan, New Jersey, kindly studied the patient's blood and confirmed our data.

during which the children were carriers of the antigen c and after a transfusion of 360 cc. of incompatible blood.

Effect of the Hemolytic Transfusion Reaction on the Anti-c Antibody Titers. The patient's serum did not contain any albumin active antibodies before the transfusion; the routine use of the "serum method"[11] for crossmatching did not reveal any incompatibility with either of the 2 bottles of blood given during surgery. It was shown, however, that the same serum contained an antibody against the antigen c which was detectable by the indirect Coombs test. This type of antibody did not disappear during the reaction. It is possible, however, that a determination of titers of this antibody would have shown a drop after the hemolytic episode. The albumin active anti-c antibody appeared on the fifth day and its titer rose to a maximum of 1:1024 on the ninth day after the reaction. At that time the patient's serum also agglutinated red blood cells of the genotype O cde/cde suspended in normal saline. The rate of fall of the anti-c titer was much slower than its rise.

TABLE 3.—ASSAY OF PATIENT'S SERUM ON A PANEL OF ERYTHROCYTES

	Type of RBC	*Agglutination*
Test 1: Patient's serum added to	A_2 CDe/cde	Positive
Test 2: Patient's serum added to	A_2B CDe/CDe	Negative
Test 3: Patient's serum added to	A_1B CDe/cde	Positive

Technique: Indirect Coombs Test.

TABLE 4.—EFFECT OF THE HEMOLYTIC TRANSFUSION REACTION ON THE ANTI-C ANTIBODY TITERS

Date	*Saline active antibodies*	*Albumin active antibodies**	*Blocking antibodies***
1 day before reaction	—	—	+
3 hours after reaction	—	—	+
1 day after reaction	—	—	+
2 days " "	—	—	+
3 " " "	—	—	+
4 " " "	—	—	+
5 " " "	—	1:2	+
6 " " "	—	1:16	+
7 " " "	—	1:128	+
8 " " "	—	1:256	+
9 " " "	1:2	1:1024	+
10 " " "	1:2	1:1024	+
11 " " "	1:2	1:1024	+
12 " " "	1:2	1:1024	+
14 " " "	1:2	1:512	+
15 " " "	1:2	1:512	+
19 " " "	—	1:256	+
34 " " "	—	1:64	+
43 " " "	—	1:32	+
83 " " "	—	1:32	+

* The term "albumin active antibodies" designates antibodies which are detectable with the "serum method" for crossmatching.

** The term "blocking antibodies" has been reserved to antibodies which can be detected only after addition of Coombs serum to erythrocytes of the genotype O, cde/cde which have been exposed to the patient's serum.

EFFECT OF THE TRANSFUSION REACTION ON RENAL FUNCTION. Figure 1 graphically represents the changes in blood urea nitrogen, creatinine and serum electrolytes over a period of 44 days after the reaction. The maximum concentration of blood urea nitrogen and creatinine was reached on the 6th day. The gradual decline of the creatinine was slower than the fall of blood urea nitrogen. By careful supervision of the serum electrolytes it was possible to avoid any excessive derangement of the ionic balance. At no time was there any decrease in urine output: the daily volume of urine ranged between 1075 and 2400 cc. during the first 15 postoperative days. The urea clearance at the time of the peak of blood urea nitrogen retention was 11.5% of normal. The hemolytic reaction was not serious enough to cause a complete renal shutdown, but obviously resulted in a fairly severe tubular injury. The absence of more severe renal damage suggests that the titer of reactive anti-c antibody cannot have been very high before the transfusions of 1000 cc. of incompatible blood.

The temporary rise in the blood pressure during surgery after starting the first bottle of blood cannot be definitely interpreted as a manifestation of the reaction because it is not typical for a sudden intravascular hemolysis: one would actually expect a drop in blood pressure. Not having any other explanation, however, for this change in vital signs one must suspect that it was in some way connected with the transfusion reaction. The lack of change in blood pressure at the time the second bottle was started, is indirect evidence that the patient's blood was then depleted of antibodies be-

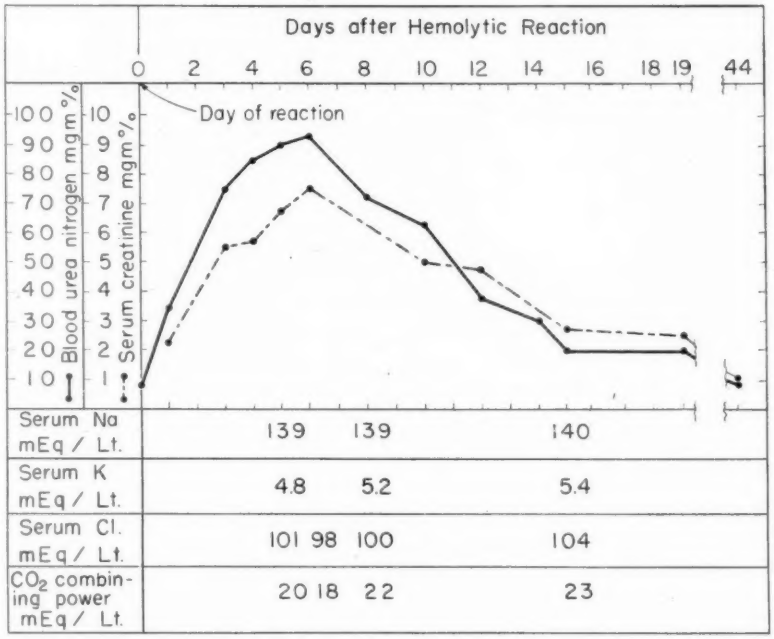
Days after Hemolytic Reaction
0 2 4 6 8 10 12 14 16 18 19 44
Day of reaction
Blood urea nitrogen mgm.%
100 90 80 70 60 50 40 30 20 10
Serum creatinine mgm.%
10 9 8 7 6 5 4 3 2 1
Serum Na mEq / Lt.
139 139 140
Serum K mEq / Lt.
4.8 5.2 5.4
Serum Cl. mEq / Lt.
101 98 100 104
CO2 combining power mEq / Lt.
20 18 22 23

FIG. 1.—Blood urea nitrogen, creatinine, and serum electrolytes after transfusion reaction.

cause they had reacted with the antigen c contained in the first bottle. Increased bleeding tendency which is the other typical manifestation of a hemolytic transfusion reaction under anesthesia, was not present in our case.

Discussion. Since Levine's original report[7] of the occurrence of the anti-hr' (anti-c) antibody a relatively small number of such cases[1-5,9,10,12-16] have been reported. This paucity is probably a consequence of the low antigenicity of the antigen c, as compared with D (Rh_0) which is the strongest antigen of the Rh group. The antigens Kell, c and E are the most frequent cause of sensitization of Rh positive mothers[8]. It is of interest that in our case none of the children ever showed evidence of erythroblastosis and the patient had a hemolytic transfusion reaction exactly 2 months after the birth of a normal child who carried the antigen c. One has to assume that the antibody did not pass through the placenta during this pregnancy, an idea which has been postulated by others in certain cases of sensitization to D.

The failure to detect the incompatibility in our case by routine crossmatching methods deserves special comment because of its practical implications. Both bottles of blood were crossmatched by the "serum method" which appears adequate to detect saline active and albumin active antibodies. The patient's serum did not contain either one of these before the transfusion. It was necessary to add Coombs serum to the donor cells after exposing them to the patient's serum in order to detect the anti-c antibody which caused the reaction. The serious complications which might arise from such an undetected incompatibility should make it imperative to perform an indirect Coombs test on every crossmatch where the recipient may have been sensitized by pregnancy or by previous intravenous or intramuscular administration of blood. In this connection it should be mentioned that 3 types of antibodies [anti-K (Kell), anti Fy^a (Duffy) and anti-JK^a (Kidd)] cannot be detected by any other technique except with the Coombs test. This obviously calls for a careful medical history especially regarding intramuscular blood injections which have been used frequently in the past for the purpose of passive immunization. This part of the medical history can be transmitted to the personnel of the blood bank on the request form for blood transfusions by simply checking the appropriate space or, more exactly, by indicating the number of pregnancies, transfusions and previous reactions. It should be possible by this method to reduce the incidence of hemolytic accidents which still occur despite the rapid progress made in recent years in the field of blood grouping.

Summary. 1. A case of hemolytic transfusion reaction caused by anti-c antibody in a multiparous woman is presented.

2. The immunization probably occurred during at least 6 out of 13 pregnancies in which the offspring was a carrier of the antigen c. The father was heterozygous for the gene C/c.

3. The incompatibility of the donor's cells with the patient's serum was not detected by routine crossmatching procedures, but could be elicited by the indirect Coombs test.

4. It is suggested that in any case where the recipient of a blood transfusion is a woman who has been pregnant or an individual who has previously received blood, an indirect Coombs test be performed on the crossmatch for detection of blocking antibodies.

The author gratefully acknowledges the technical assistance of Miss Eileen Blomquist.

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THE VALUE OF ORAL TERRAMYCIN IN PRE-OPERATIVE PREPARATION OF THE GUT*

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In a study of oral dihydrostreptomycin as an intestinal disinfectant[2] supplementary treatment with terramycin was used in 2 cases. The results of this encouraged a study of the fecal flora in an additional 8 cases treated with terramycin only. Of the 10 patients, 4 had no gastrointestinal disease, 4 had malignant disease of the large bowel and 2 had ulcerative colitis of unknown cause. Five of the patients studied underwent surgical operation on the bowel.

Experimental Methods. Samples of feces were obtained at short intervals from the patients, before, during and after treatment, and the effect was evaluated by colony counts of aerobic and anaerobic growth, with isolation and identification of selected species of bacteria. A profuse growth of Proteus often occurred in the course of therapy, resulting in a large count of Gram-negative organisms, not infrequently larger than the original baseline counts. The swarming growth of Proteus tended to mask the other bacteria and made accurate counting and identification very difficult. In 3 patients of this series, Proteus was found in pretreatment specimens.

Quantitative Analysis. Quantitative analysis of each fecal specimen was performed as follows: An original suspension of feces was made in sterile distilled water to give a 1:10 dilution by weight (9 cc. of water per gram of feces). This suspension was thoroughly mixed by mechanical shaking and a series of 10-fold dilutions was made in sterile distilled water so that the last tube was 10^{-12} of the concentration of the original fecal specimen.

From each tube of this series, three 0.05 cc. samples were distributed evenly with a platinum wire spreader over the surface of one MacConkey plate and 2 blood agar plates. The McConkey plate and one blood agar plate were incubated aerobically and the other blood agar plate anaerobically at 37°C. The method used for obtaining anaerobic conditions was a modification of the McIntosh and Fildes anaerobic jar.

After 24 hours' incubation, the following determinations on the aerobic cultures were recorded: (1) the total number of coliform-like colonies (members of the coli-aerogenes group); (2) the total number of proteus organisms; (3) the total number of all other bacteria growing aerobically. After 48 hours the plates were checked for the appearance of any new colonies. The total number of all organisms growing on the anaerobic blood agar plates was counted after 4 days incubation, and checked after 8 days. Knowing the total number of all organisms growing aerobically, the number of anaerobic organisms could then be calculated. In addition, the approximate numbers of the different recognizable types of colonies present were noted, both aerobically and anaerobically.

Qualitative Analysis. In the qualitative analysis the various aerobic species occurring in the feces were isolated and identified, using the classification in Bergey's Manual of Determinative Bacteriology[2]. The different types of anaerobic species were studied by colony, appearance on plates, morphology in Gram-stained films and for absence of growth on an aerobic blood agar slope. It was found in our work with dihydrostreptomycin[3] that the thorough identification of all the anaerobic species occurring in the feces involved more time and material than was practical in such an extensive survey of fecal specimens. Also in 5 of the cases, Proteus appeared in very

* This work was made possible by a grant from the Merck and Co., Ltd. and the Terramycin was supplied by Pfizer and Company.

large numbers and their swarming growth made isolation in pure culture of the anaerobic colonies extremely difficult. On the basis of their appearance on plates and in stained smears, the anaerobic bacteria were divided as follows:

(1) Small grey relatively smooth colonies,
  (a) small Gram-negative rods: *Bacteroides* sp.
  (b) Gram-positive thin rods or filaments: *Lactobacillus* sp.
  (c) Gram-positive cocci: Anaerobic cocci.
(2) Smooth colonies with target hemolysis: *Cl. perfringens.*
(3) Small black pigmented colonies (Gram-negative rods): *B. melaninogenicus.*

SENSITIVITIES. The antibacterial activity of terramycin was tested against all the various aerobic organisms isolated. A series of halving dilutions of terramycin with an original concentration of 250 mcg. per cc. was used to determine the sensitivity of each organism.

Results. In reviewing the findings of the experimental work in this study, each patient is discussed briefly and graphs and tables of the more interesting cases are presented. The results of the sensitivity tests of the various types of bacteria to terramycin can be summed up as follows: Coliform usually quite sensitive and inhibited by between 2 and 16 mcg. per cc.; *Paracolobactrum* and *Achromobacter* only very slightly sensitive, approximately 125 to 250 mcg. per cc. prevented growth; *Proteus* and *Pseudomonas* insensitive; grew in 250 mcg. per cc.; some species of micrococci and of enterococci were slightly sensitive while others proved highly resistant.

Case Reports. CASE 1. Patient W. L., female, aged 51, suffering from ulcerative colitis, was in hospital for investigation and medical therapy.

She received dihydrostreptomycin for 5 days, sulfathaladine on the 4th and 5th days, and terramycin, 4 gm. daily for 2 days after the other two drugs were discontinued.

The coliform count was not reduced by dihydrostreptomycin alone but actually increased in numbers. The addition of sulfathaladine caused a decrease in the coliform count to the pretreatment level. The replacement of these 2 drugs by terramycin caused the drop in coliform count to continue, and in 2 days the terramycin had eliminated all coliform bacteria from the feces. Dihydrostreptomycin reduced the numbers of other aerobic bacteria temporarily, but they soon returned to the original level, and the addition of sulfathaladine and of terramycin had no effect. The anaerobic count was unaffected by dihydrostreptomycin alone or in combination with sulfathaladine, but terramycin eliminated the anaerobes from the feces.

COMMENT. This dose of terramycin was very effective in simplifying the fecal flora but caused comparatively little reduction in total numbers.

Graph 1 and Table 1 show the fluctuations in counts and in types of bacteria isolated.

CASE 2. Patient M. S., female, aged 31, had acute peritonitis of 4 days' duration resulting from a perforation due to carcinoma of the sigmoid colon. The peritoneal cavity was drained, and later an abdomino-perineal resection was done.

She was given dihydrostreptomycin for 6 days, and terramycin, 1 gm. daily for 2 days, beginning 10 days after dihydrostreptomycin had been discontinued.

Dihydrostreptomycin had little effect upon the coliform or anaerobic counts, but after 5 days the aerobic Gram-positive cocci were reduced in numbers. The aerobic count returned to the pretreatment level when the drug was discontinued, and terramycin was ineffective in lowering it as large numbers of terramycin-resistant *Staphylococcus pyogenes* and other micrococci persisted. Terramycin reduced the numbers of both coliform and anaerobic species.

COMMENT. Terramycin reduced the coliforms and anaerobes to some extent, but it had no effect upon the aerobic cocci present in very large numbers.

Graph 2 and Table 2 show the fluctuations in counts and in types of bacteria isolated.

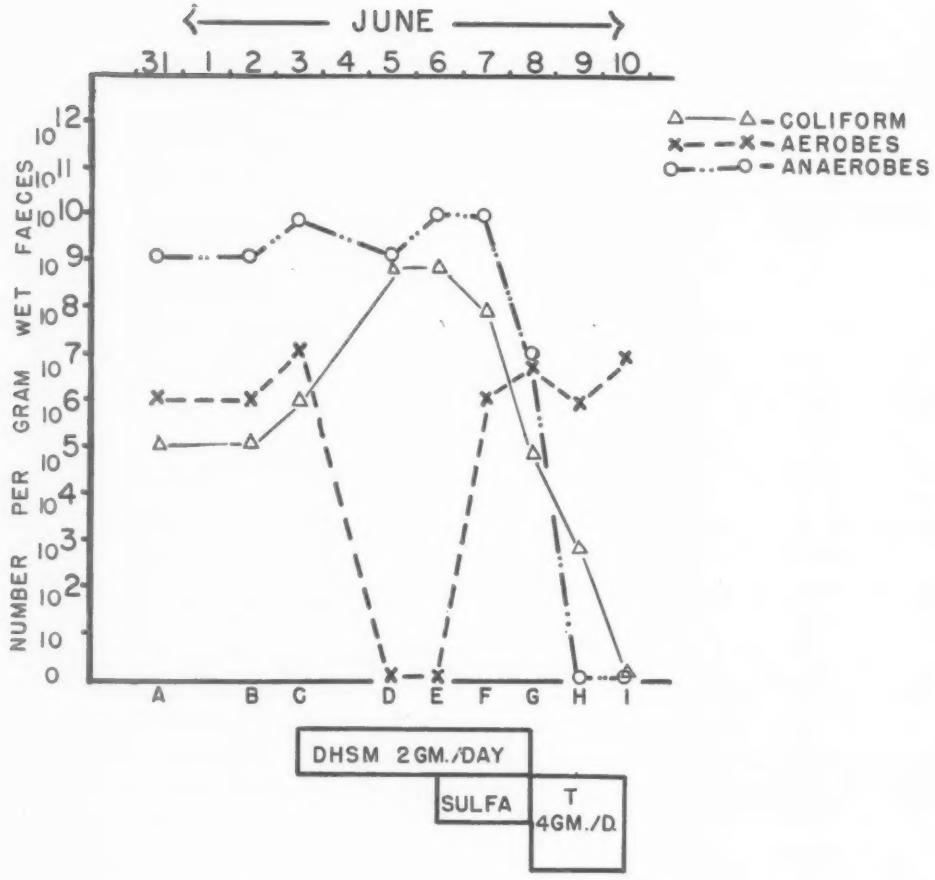
CASE 3. Patient H. D., male, aged 59, had adenocarcinoma of the rectum that was treated by proctosigmoidectomy.

He received terramycin, 1.5 gm. daily (250 mg. every 4 hours) for 2 days.

Terramycin produced a very slight drop in the coliform and anaerobic counts in 2

GRAPH 1

CASE 1 (*W. L. ♀ 51*) *Ulcerative Colitis*
Effect of Medication of Fecal Bacteria
DHSM=Dihydrostreptomycin
Sulfa=Sulfathalidine
T=Terramycin



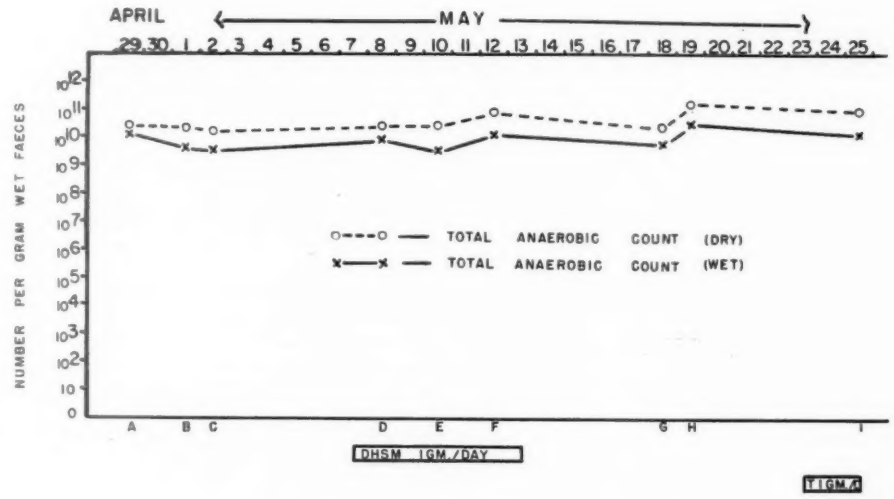
W.L. ♀ 51 ULCERATIVE COLITIS

TABLE 1.—CASE 1 (PATIENT W. L.) EFFECT OF TERRAMYCIN (JUNE 8 TO JUNE 10), DIHYDROSTREPTOMYCIN (JUNE 3 TO JUNE 8) AND SULFATHALADINE (JUNE 6 TO JUNE 8)

Organisms Isolated	*Sensitivity to Terramycin mcg./cc.*	*Approximate Nos/Gm. Feces* (a) 31/5	(b) 2/6	(c) 3/6	(d) 5/6	(e) 6/6	(f) 7/6	(g) 8/6	(h) 9/6	(i) 10/6
AEROBIC										
E. coli grunthali	–	10^5	10^5	10^6	—	—	—	—	—	—
E. coli commune	–	10^4	10^5	10^6	—	—	—	—	—	—
E. coli neapolitana	–	10^4	—	—	—	—	—	—	—	—
A. aerogenes	8	10^3	—	10^6	10^9	10^9	10^8	10^5	10^3	—
Paracolobactrum intermedium	–	10^2	—	10^4	—	—	—	—	—	—
Non-hemolytic enterococci	4	10^6	10^6	10^7	—	—	10^6	10^7	10^6	10^5
Hemolytic enterococci	–	—	—	10^5	—	—	—	—	—	—
Staph. pyogenes	–	10^6	10^3	—	—	—	—	—	—	—
Yeast-like fungus	–	—	—	—	—	—	—	10^3	10^4	10^7
ANAEROBIC										
Bacteroides sp.		10^9	10^9	10^9	10^9	10^{10}	10^{10}	10^7	—	—
Lactobacillus sp.		10^7	10^7	10^9	10^8	10^8	10^{10}	10^6	—	—
B. melaninogenicus		10^3	10^4	10^4	—	—	—	—	—	—
Cl. perfringens		10^4	10^4	10^2	10^5	10^4	—	—	—	—
Anaerobic cocci		10^5	10^6	10^7	10^6	10^4	10^7	—	—	—

GRAPH 2

CASE 2.—Effect of Medication on Fecal Bacteria
DHSM=Dihydrostreptomycin
T=Terramycin



M.S. ♀ 31 CANCER OF SIGMOID

TABLE 2.—CASE 2 (PATIENT M. S.) EFFECT OF ORAL TERRAMYCIN (MAY 23 TO MAY 25) AND ORAL DIHYDROSTREPTOMYCIN (MAY 7 TO MAY 13)

Organisms Isolated	*Sensitivity to Terramycin mcg./cc.*	*Approximate Nos/Gm. of Feces* (a) 29/4	(b) 1 5	(c) 2/5	(d) 8 5	(e) 10/5	(f) 12/5	(g) 18/5	(h) 19/5	(i) 25/5
AEROBIC										
E. coli acidi lactici	–	10^9	10^9	10^8	—	—	—	—	—	—
E. coli immobile	–	10^8	—	—	10^7	—	—	—	—	—
E. coli communior	–	10^8	10^8	—	—	—	—	10^8	10^8	—
E. coli grunthali	4	—	10^8	10^9	—	—	—	10^8	10^8	10^3
A. aerogenes	8	10^4	10^5	10^4	10^5	10^7	10^8	10^7	10^8	10^3
Paracolobactrum coliforme	4	10^7	10^7	10^7	10^8	10^8	10^9	10^9	10^{10}	10^5
Pseudomonas	125	—	—	—	—	—	—	—	—	10^5
Alk. faecalis	–	10^4	—	—	—	—	—	—	—	—
Non-hemolytic enterococci	–	10^9	10^9	10^9	10^7	10^7	—	10^9	10^{10}	—
Micrococci	not sens. to 250	—	—	—	—	10^6	—	—	—	10^9
Staph. pyogenes	not sens. to 250	—	—	—	—	—	—	—	—	10^{10}
ANAEROBIC										
Bacteroides sp.		10^{10}	10^9	10^9	10^9	10^9	10^{10}	10^9	10^9	—
Lactobacillus sp.		10^8	10^9	10^9	10^9	10^9	10^9	10^7	10^7	—
B. melaninogenicus		10^6	—	—	10^4	10^3	—	10^5	10^6	—
Cl. perfringens		10^5	10^5	10^5	—	10^5	10^4	10^3	10^5	10^4
Anaerobic cocci		10^8	—	10^5	10^5	—	—	—	—	—

days. The enterococci, which were only moderately sensitive to the drug, had none the less been eliminated after one day's dosage.

COMMENT. Relatively little effect was noted in this case.

CASE 4. Patient G. H., female, aged 42, used as a control, had a laparotomy for abdominal adhesions following an appendectomy.

She was given terramycin, 1.5 gm. daily (250 mg. every 4 hours) for 2 days.

Terramycin had no effect in reducing the total numbers of coliform or anaerobic species. In fact, a swarming *Proteus* organism, present in the pretreatment specimens, increased in number after 2 days on terramycin, giving a total Gram-negative count considerably higher than that in the pretreatment specimens. The moderately sensitive enterococci were suppressed, but reappeared in very large numbers 3 days after the terramycin had been withdrawn.

COMMENT. The total numbers of bacteria present actually showed a slight increase in this patient, and the terramycin cannot be considered to have been beneficial in simplifying the flora.

CASE 6. Patient A. L., female, aged 44, had cancer of the rectum, treated by colostomy.

She was given terramycin, 2 gm. daily (500 mg. every 6 hours) for 2 days.

Terramycin produced decided reductions in the coliform, aerobic and anaerobic counts after 2 days.

COMMENT. Terramycin was of benefit in reducing the coliform flora in this patient, and lowered the total count after 2 days.

Graph 3 and Table 3 show the reductions in counts and the simplification of types of bacteria present.

CASE 7. Patient M. N., female, aged 53, used as a control, had cystitis.

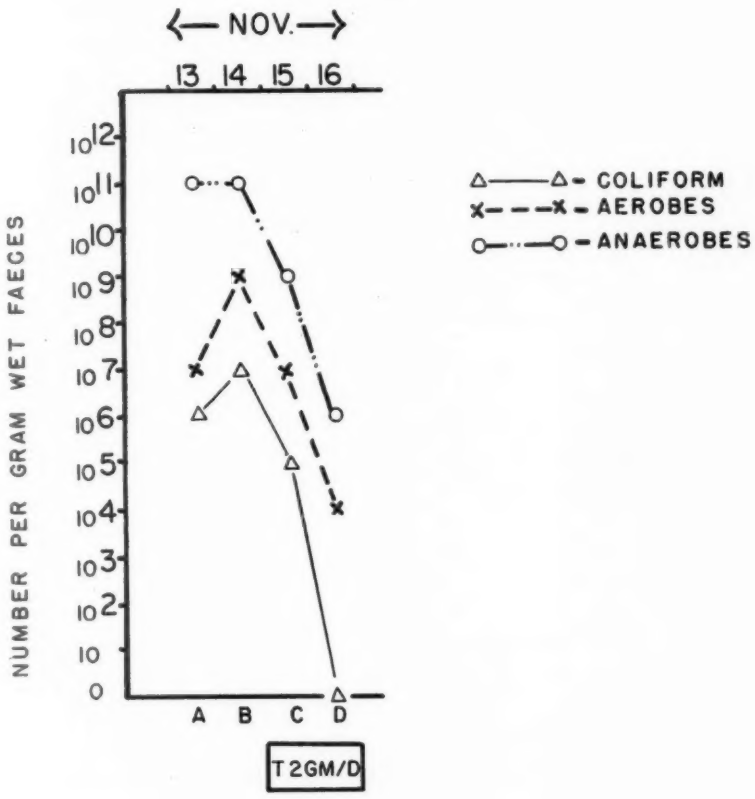
She received terramycin, 2 gm. daily (500 (mg. every 6 hours) for 2 days.

Terramycin eliminated the coliform and other aerobes. However, large numbers of *Proteus* appeared on the second day of the terramycin therapy, giving a total Gram-negative count far higher than that in the pretreatment specimen. Little effect was produced on the anaerobic flora.

COMMENT. The terramycin was of no value in lowering the total bacterial counts.

GRAPH 3

CASE 6 (*A. L. ♀ 4*) *Cancer of Rectum*
Effect of Medication on Fecal Bacteria
T=Terramycin



A.L. ♂24 REGIONAL ENTERITIS

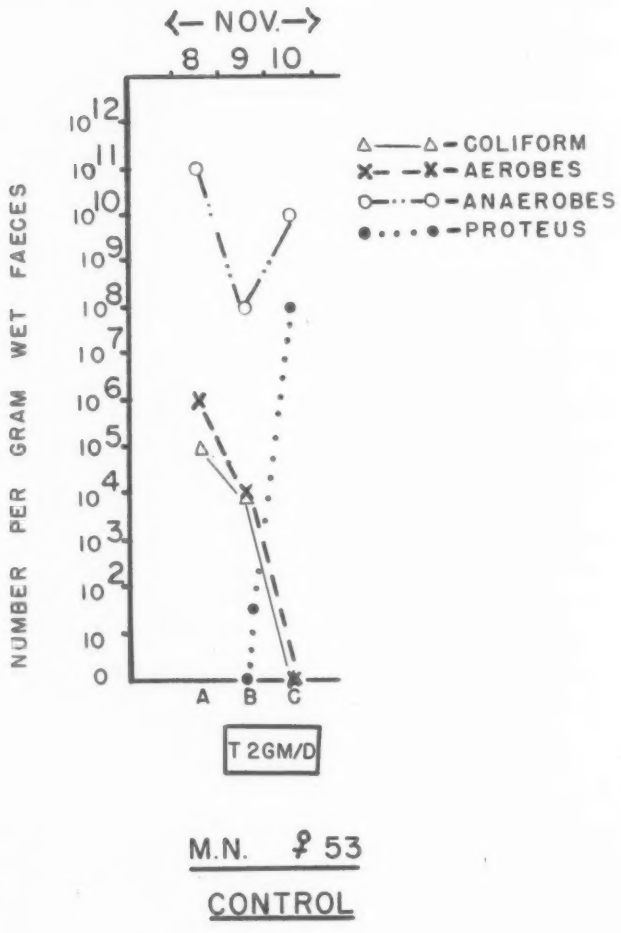
TABLE 3.—CASE 6 (PATIENT A. L.) EFFECTS OF TERRAMYCIN (NOVEMBER 15 TO NOVEMBER 16)

Organisms Isolated	*Sensitivity to Terramycin mcg./cc.*	*Approximate Nos/Gm. Feces* (a) *13/11*	(b) *14 11*	(c) *15/11*	(d) *16/11*
AEROBIC					
E. coli grunthali	16	10^6	10^7	10^5	—
E. coli acidi lactici	8	10^5	10^6	10^4	—
A. aerogenes	2	10^4	—	—	—
Pseudomonas	not sens. to	—	—	—	10^2
Achromobacter	125	10^6	10^5	10^3	—
Non-hemolytic enterococci	31	10^7	10^9	10^6	10^4
Hemolytic enterococci	16	10^7	10^8	10^7	10^4
Aerobic spore-former		10^3	10^2	10^3	—
ANAEROBIC					
Bacteroides sp.		10^{11}	10^{11}	10^9	10^4
Lactobacillus sp.		10^{10}	10^{10}	10^8	10^6
B. melaninogenicus		10^7	10^6	10^7	10^4
Cl. perfringens		10^4	—	—	—
Anaerobic cocci		10^{11}	—	—	10^5

Graph 4 and Table 4 show the fluctuations in counts and types of bacteria isolated.

CASE 8. Patient F. F., male, aged 32, used as a control, had a traumatic amputation of the leg with gas gangrene.

GRAPH 4
Effect of Medication on Fecal Bacteria
T=Terramycin



He received terramycin, 2 gm. daily (500 mg. every 6 hours) for 9 days, and 1 gm. daily (250 mg. every 6 hours) for 6 days. The terramycin eliminated the coliform bacteria from the feces and kept them suppressed even though the daily dose was reduced after 9 days. The coliforms returned to pretreatment levels when the drug was discontinued, and at the same time *Proteus* organisms made their first appearance. The other aerobic organisms, all of which were relatively resistant to terramycin, showed an increase in numbers. The anaerobes were reduced in number and after the 16th day of therapy none were isolated from the feces.

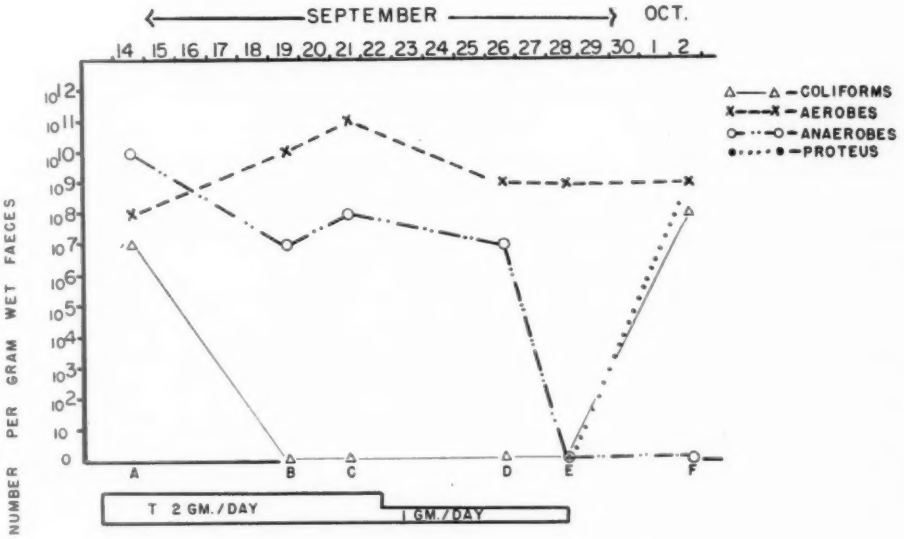
COMMENT. Terramycin reduced both the coliform and anaerobic bacteria, but the numbers of other aerobic

TABLE 4.—CASE 7 (PATIENT M. N.) EFFECT OF TERRAMYCIN (NOVEMBER 9 TO NOVEMBER 10)

Organisms Isolated	*Sensitivity to Terramycin mcg./cc.*	*Approximate Nos/Gm. Feces* (a) 8/11	(b) 9/11	(c) 10/11
AEROBIC				
E. coli acidi lactici	2	10^5	10^3	—
E. coli coscoroba	8	10^5	10^3	—
E. coli grunthali	8	—	10^4	—
A. aerogenes	8	10^4	10^2	—
Paracolobactrum coliforme	125	10^4	10^2	—
Proteus morgani	not sens. to 250 mcg/ml.	—	—	10^8
Proteus vulgaris	not sens. to 250 mcg/ml.	—	—	10^7
Non-hemolytic enterococci	31	10^4	10^3	—
Hemolytic enterococci	31	10^6	10^4	—
ANAEROBIC				
Bacteroides sp.		10^{11}	10^8	10^{10}
Lactobacillus sp.		10^{11}	10^7	—
B. melaninogenicus		10^8	—	—
Anaerobic cocci		10^{10}	10^8	—

GRAPH 5

Effect of Medication on Fecal Bacteria
T=Terramycin



F.F. ♂ 32 TRAUMATIC AMPUTATION OF LEG
GAS GANGRENE

bacteria remained at a high level throughout therapy.

Graph 5 and Table 5 show the fluctuations in counts and types of bacteria isolated.

CASE 9. Patient O. B., male, aged 41, had lymphosarcoma, and was treated by total colectomy.

He received terramycin 3 gm. daily (500 mg. every 4 hours) for 5 days before operation. Three days later, daily terramycin, 500 mg., 4th hour, was recommended and continued for 8 days.

CASE 10. Patient F. S., female, aged 20, had ulcerative colitis. There was performed a closure of a previous transverse colostomy with anastomosis of the transverse colon to the anus with sphincter preservation.

She was given terramycin, 3 gm. daily (500 mg. every 4 hours) for 7 days.

Terramycin suppressed the coliform bacteria irregularly but *Proteus*, which was present in one of the pretreatment specimens, persisted, so that the total Gram-negative count was very little below that of the pretreatment specimens. Little effect was produced on the other aerobic bacteria, and their

TABLE 5.—CASE 8 (PATIENT F. F.) EFFECT OF TERRAMYCIN (SEPTEMBER 13 TO SEPTEMBER 28)

Organisms Isolated	*Sensitivity to Terramycin mcg./cc.*	*Approximate Nos/Gm. Feces* (a) 14/9	(b) 19/9	(c) 21/9	(d) 26/9	(e) 28/9	(f) 2/10
AEROBIC							
E. coli grunthali	2	10^7	—	—	—	—	—
E. coli freundii	8	10^5	—	—	—	—	10^8
A. aerogenes	8	—	—	—	—	—	10^8
Proteus morgani	250	—	—	—	—	—	10^9
Proteus vulgaris	not sens. to 250 mcg./ml.	—	—	—	—	—	10^9
Achromobacter	62	—	—	10^9	10^9	10^9	10^6
Non-hemolytic enterococci	250	10^6	10^{10}	10^{11}	10^9	10^9	10^9
Hemolytic enterococci	125	10^8	—	10^8	—	10^8	10^8
Aerobic spore-former		10^3	—	—	—	—	—
Yeast-like fungus		—	10^5	—	—	—	—
ANAEROBIC							
Bacteroides sp.		10^{10}	10^7	10^8	10^7	—	—
Lactobacillus sp.		10^{10}	—	—	—	—	—
B. melaninogenicus		10^5	10^4	—	—	—	—
Cl. perfringens		10^4	—	—	—	—	—

In this patient, *Proteus* was present in the pretreatment specimens, and continued to appear in large numbers throughout therapy. The coliform counts showed some reduction in numbers during the first course of the drug. During the second series of doses, the coliform bacteria were eliminated, but the overall Gram-negative count remained at a very high level. There was little fluctuation in the anaerobic count in this patient. No Gram-positive aerobic bacteria appeared in the feces until the second course of the terramycin, when moderately sensitive micrococci were isolated.

COMMENT. The terramycin was of little benefit in this case and the large numbers of swarming *Proteus* made accurate counting difficult.

counts remained high throughout the therapy. A slight reduction in the anaerobic count occurred.

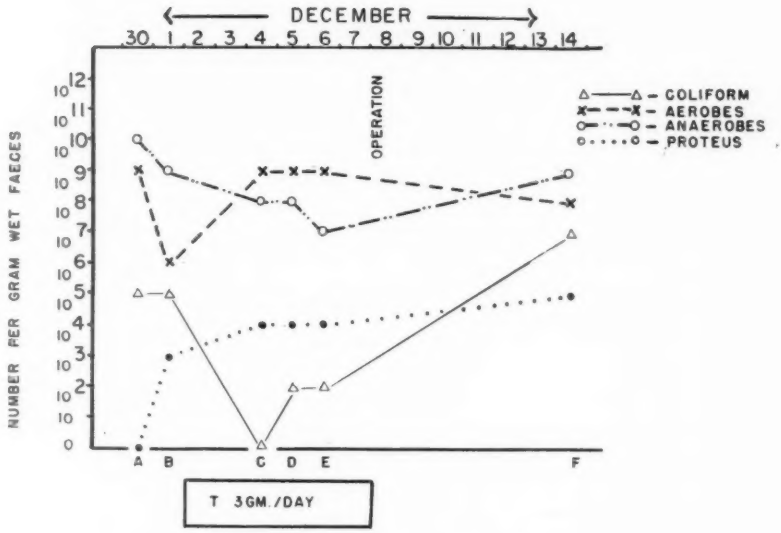
COMMENT. Although the coliform count was reduced, the terramycin was not of much value in this patient as the total numbers of bacteria remained high throughout the course of the drug.

Graph 6 and Table 6 show the fluctuations in counts and in types of bacteria isolated.

In order to present these results in a more compact form, a statistical analysis was made of all the pretreatment counts aerobic, anaerobic, and

GRAPH 6

Effect of Medication on Fecal Bacteria
T=Terramycin



F.S. ♀ 20 ULCERATIVE COLITIS

TABLE 6.—CASE 10 (PATIENT F. S.) EFFECT OF TERRAMYCIN (DECEMBER 3 TO DECEMBER 7)

Organisms Isolated	*Sensitivity to Terramycin mcg./cc.*	*Approximate Nos/Gm. Feces* (a) 30/11	(b) 1/12	(c) 4/12	(d) 5/12	(e) 6/12	(f) 14/12
AEROBIC							
E. intermedium	8	10^5	10^4	—	10^2	—	10^7
E. coli grunthali	4	—	10^5	—	—	—	—
A. aerogenes	16	10^4	10^2	—	—	10^2	10^8
Proteus mirabilis	250	—	10^3	10^4	—	10^4	10^8
Achromobacter	31	10^3	—	—	—	—	—
Non-hemolytic enterococci	62	10^9	10^6	10^8	10^9	10^9	10^8
Hemolytic enterococci	31	10^7	10^6	10^9	—	—	—
Micrococci	16	10^5	10^6	—	10^9	10^9	10^6
Gram-positive non-sporing rods	16	10^6	—	—	—	—	—
ANAEROBIC							
Bacteroides sp.		10^{10}	10^9	10^8	10^8	10^7	10^9
Lactobacillus sp.		10^9	10^9	—	—	—	10^8
Anaerobic cocci		—	—	—	—	—	10^8

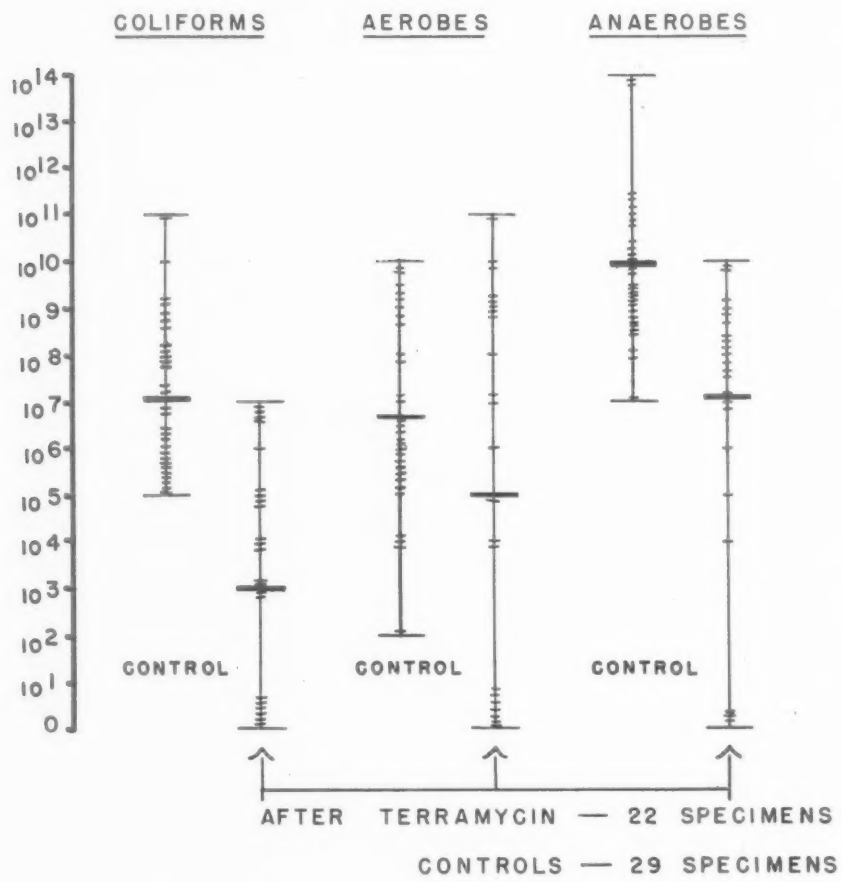
coliform in this series of cases, which amounted to 29 specimens. These were plotted on the same scale as the previous graphs, and the arithmetical mean of these values was taken. The specimens taken during the course of treatment were dealt with in the same manner; these amounted in all to 22 specimens, which were quantitatively analysed for coliforms, other aerobes, and anaerobes.

The results are shown in Graph 7. It is interesting that the T-test applied to these figures shows statistical significance in the reduction of the coliforms, but not in the other 2 groups.

(Coliform: $t=6.0419$ 49 df.)
(Aerobes: $t=2.0964$ 49 df.)
(Anaerobes: $t=1.2281$ 49 df.)

Discussion. The actual effect of terramycin alone for the reduction of the fecal flora is undesirable. Although there is reduction in the numbers and species of coliforms, the total bacterial counts remain at high levels, even with large doses of 2 or 3 gm. a day. The alteration in the flora is probably a serious disadvantage, because antibiotic-resistant *Proteus* and *Pseudo-*

GRAPH 7



monas appear in a great many of the cases and completely dominate the fecal flora.

Is it really desirable to alter the flora? The natural organisms found in the bowel serve many useful purposes. They maintain among themselves an established balance, which keeps in check invasion by more troublesome organisms. Point is given to this remark and support to our findings by a recent paper of Sieburth, McGinnis, and Skinner[4] who show that a terramycin supplement to the diet of turkey poults gave rise to abundant development of *Proteus mirabilis* in their gut. The antibiotic greatly reduced *Escherichia coli, Streptococcus faecalis* and *Streptococcus liquifaciens* which were identified as *Proteus* antagonists by their direct inhibition of growth on agar plates. Furthermore, our results conform with those of Baker and Pulaski[1] using terramycin orally in human cases.

The bacteriological evidence does not confirm the clinical results that have obtained in pre-operative preparation of the bowel, namely, a marked decrease in peritonitis, and fewer post-operative complications. The sense of security this use of antibiotics inspired may have encouraged surgeons to do more radical operations, with special care for post-operative treatment, resulting in a lower mortality rate and a better appreciation of operable cases. For example, the open end-to-end anastomosis is more satisfactory than the so called closed aseptic technique, whether antibiotics are used or not, particularly in carcinoma of the colon. In ulcerative colitis, surgery has swung to ileostomy combined with subtotal colectomy rather than a more timid series of resections.

Conclusion. (1) Terramycin alone in small doses may affect the coliform and other aerobes, but the results are uncertain and variable. A dose of 1.5 gm. seems too small to be useful.

(2) In larger doses, 2 and 3 gm. daily, the reduction in counts occurred more often, but some resistant organisms always persisted to keep the total number of bacteria present at a high level.

(3) The frequent occurrence of large numbers of *Proteus*, which were resistant to terramycin, was often the cause of the reversion in total counts.

(4) Terramycin used alone does not seem to be an ideal intestinal antiseptic.

(5) It would seem that attempts at complete control of the fecal flora are extremely difficult. As soon as one organism disappears, others take its place, and these are often more resistant ones which are more difficult to deal with should a post-operative complication occur.

(6) To concentrate on only one group of organisms, such as the coliforms, and ignore the other flora of the bowel is deceptive and does not give a true picture of the actual situation.

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COMPARISON OF RESULTS OF TREATMENT OF PNEUMOCOCCIC INFECTIONS IN MICE WITH MULTIPLE DOSES OF AUREOMYCIN AND PENICILLIN COMBINED COMPARED WITH EACH DRUG ALONE

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In a study[6] of the treatment of mice infected with pneumococci with a combination of one dose of penicillin and one dose of aureomycin it was shown that the therapeutic results were sometimes better than, sometimes worse than, and sometimes equal to the results obtained with penicillin alone. Whether the additive or antagonistic effect was demonstrable depended on the effectiveness of each drug and the time relationship of each of the drugs to the other.

Ahern, Burnell, and Kirby[1] have reported that in mice with a streptococcal infection chloramphenicol reduced the efficiency of penicillin when just one dose of both drugs was used, but when several doses of each of the drugs were given each day over a 3-day period, no antagonism was demonstated.

In the present paper evidence is presented that aureomycin may be antagonistic to or additive with penicillin when the drugs are administered in multiple doses to mice with pneumococcic infections.

Method. The procedure followed was essentially the same as that reported previously[6]. In each experiment the mice were divided into 3 groups: one group received penicillin, one aureomycin, and the third penicillin plus aureomycin according to the same dose and the time schedule. Whenever a new drug schedule was introduced uninfected animals were given the drugs to preclude drug toxicity as the cause of death.

In 9 experiments the animals were treated with the drugs at 4-hour intervals for 10 injections. In 11 experiments aureomycin was administered only once and the penicillin once a day for 3 days. In all other experiments each drug was given once a day for 3 days. The time relationships of the inoculation of pneumococci and the injections of each of the drugs were varied in several different ways, as explained in the text.

Differences in the fatality rates in each experiment were tested for significance by the chi square method. Statistically significant antagonism was considered to be present when the number of deaths in mice receiving the combination was sufficiently greater than the number in mice treated with penicillin alone so that the probability of chance occurrence was less than 5%. If the number of deaths in the combination group was similarly lower than the number in either the penicillin or the aureomycin group, significant addition was recorded.

In further analysis of the data, all comparisons were made in terms of the percentage of total experiments in any group which showed significant antagonism and addition. The sum of the individual doses given during the 3-day period was used as the basis for consideration of the effect of the dose of each antibiotic on the outcome of the experiment.

Results. One hundred and twelve experiments were performed. In 19, penicillin was given 4 hours before aureomycin. Among the other 93 experiments in which aureomycin and penicillin were given concurrently or in which aureomycin preceded penicillin, 20 each (21.2%) showed significant antagonism or addition. Thus, 42.4% of the experiments showed one of the 2 phenomena whereas in 57.6% no significant effect upon the action of penicillin was demonstrated by the addition of aureomycin.

EFFECT OF DOSE OF DRUGS. Some experiments showed significant antagonism and some showed significant addition when treatment was started at any time interval from just before to 12 hours after infection. For this reason, in the subsequent analyses, the experiments have been considered together regardless of the duration of infection before treatment.

The most important factor in determining whether antagonism or addition occurred in a given experiment was the amount of each antibiotic used. Figure 1 illustrates that among 17 experiments, when the initial dose of aureomycin was given 4 hours before the first dose of penicillin and the dose of aureomycin was low, antagonism occurred in 26.6% of the experiments and addition in none. On the other hand, among the 15 experiments where the dose of aureomycin was high none showed antagonism and 46.7% showed addition. The percentage of experiments in which significant

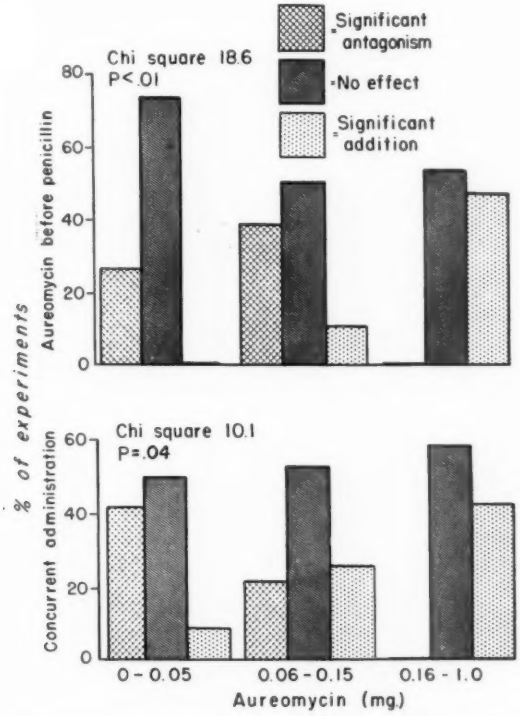

FIG. 1.—Relation of percentage of experiments in which significant antagonism and addition were demonstrated to the dose of aureomycin.

addition occurred might actually have been higher if it had been possible to measure therapeutic efficiency above a 100% survival rate. Among the 18 experiments in an intermediate dosage range, 38.9% showed antagonism and 11.1% showed addition.

When aureomycin and penicillin were administered concurrently, and showed antagonism or addition. As indicated in Fig. 1, this distribution is highly significant by the chi square test.

Figure 2 shows a similar analysis for penicillin. When the dose of penicillin was high, antagonism occurred in 33% of the 12 experiments in which aureomycin preceded penicillin and in 29.3%

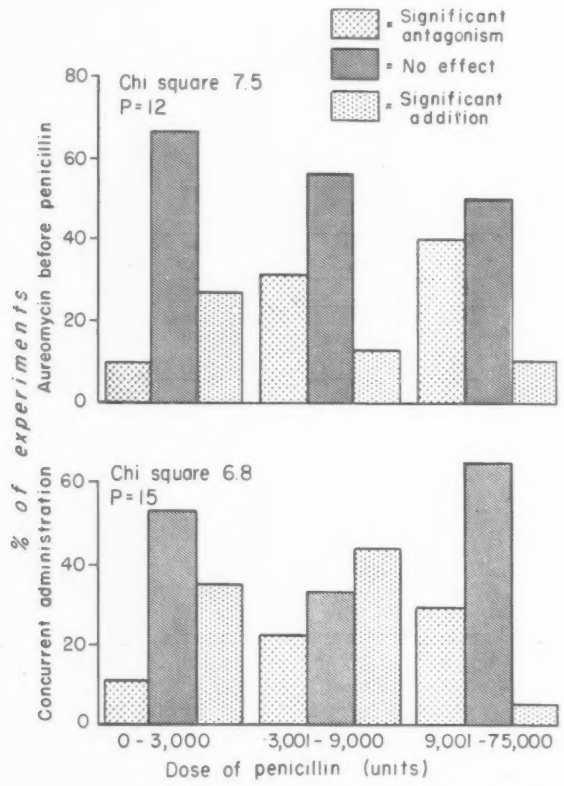

FIG. 2.—Relation of percentage of experiments in which significant antagonism and addition were demonstrated to the dose of penicillin.

the dosage range of aureomycin was low, 41.7% of 12 experiments showed antagonism and 8.2% addition. Among 12 experiments in which the dose of aureomycin was high none showed antagonism and 41.7% showed addition. Among 19 experiments in which intermediate doses of aureomycin were given, 21.6% and 26.3%, respectively, of the 17 experiments in which the 2 were given concurrently, while addition occurred in 8.3% and 5.9% respectively. With the lowest penicillin doses there were 22 experiments in the group in which aureomycin preceded penicillin and 17 in the group in which the drugs were given concurrently. In these groups, antagonism was demon-

strated in only 9.1% and 11.7% of the experiments, and addition in 27.2% and 35.4%, respectively. This distribution was not statistically significant when based on the number of experiments performed.

As has been shown in Figs. 1 and 2, a definite point of separation between the experiments which showed significant addition or significant antagonism could not be obtained when the data were tabulated according to the dosage range of either antibiotic. Figure 3, on the other hand, demonstrates that the separation between addition and antagonism was more precise when the tabulation was made according to the ratio of the dose of penicillin to the dose of aureomycin. When each dose of aureomycin was administered 4 hours before a dose of penicillin there was antagonism in 4% of 25 experiments, 47.6% of 21 experiments, and none in 4 experiments in the lowest, medium, and highest ratio groups, respectively. Addition occurred in 35% of the lowest ratio group and in neither of the other groups. In the experiments in which the drugs were given concurrently, in the low ratio group there was 57.2% addition and no antagonism among 14 experiments. In the intermediate group 14.2% of the 21 experiments showed addition and 28.5% showed antagonism. Among 8 experiments in the high ratio group, 37.5% antagonism and no addition were demonstrated. These distributions were statistically significant.

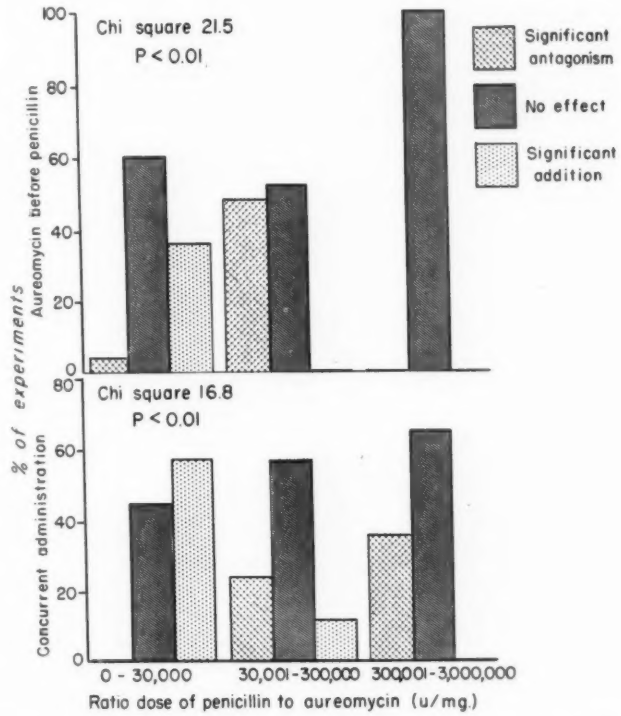

FIG. 3.—Percentage of experiments in which significant antagonism and addition were demonstrated in different penicillin-aureomycin dose ratio.

When the therapeutic effectiveness of the drugs rather than the dose is considered the point of separation between addition and antagonism is still more clearly seen. In Table 1 the data are arranged according to the ratios of the mean survival days of infected mice treated with aureomycin to the mean survival days of those treated with penicillin. When this ratio was low, only antagonism occurred. In the group where this ratio was 0 to 0.9, antagonism occurred in 50% of the experiments in which the antibiotics were administered at the same time, and in 17.6% of those in which aureomycin preceded penicillin. In the group where the ratio was .10 to .19, only antagonism was seen and this was present in approximately three-fifths of the experiments. In the group where the ratio was .20 to .39 antagonism was observed less often and addition made an appearance among the experiments where the antibiotics were administered concurrently. As the ratio increased in magnitude, antagonism rapidly disappeared and addition occurred in as high as 90% of the experiments. This distribution also was highly significant. Thus, if the data are refined, one can define quite clearly when antagonism may be expected and when addition may be expected. The large number of experiments in the very low ratio group, in which neither addition nor antagonism was found, was apparently due to the use of doses of aureomycin that were too low to cause any effect at all, and the high percentage of similar results in the middle range of ratios may well represent the concurrence of the 2 phenomena which neutralized each other.

TABLE 1.—RELATION BETWEEN THE PERCENTAGE OF EXPERIMENTS IN WHICH SIGNIFICANT ANTAGONISM OR ADDITION WAS FOUND AND THE RATIO OF DURATION OF SURVIVAL FOLLOWING AUREOMYCIN TO THAT FOLLOWING PENICILLIN

Time Relationship of Aureomycin to Penicillin	*Ratio of Mean Survvial Day of Aureomycin to Mean Survival Day of Penicillin*	*Experiments Which Showed:*						
		Significant Antagonism		*No Effect**		*Significant Addition*		
		Number	*%*	*Number*	*%*	*Number*	*%*	*Tota*
Aureomycin	0 –0.09	3	17.6	14	82.4	0	0	17
	0.1 –0.19	4	66.7	2	33.3	0	0	6
Administered	0.20–0.39	3	50.0	3	50.0	0	0	6
	0.4 –0.69	1	16.7	5	83.3	0	0	6
Before	0.70–1.09	0	0	1	20.0	4	80.0	5
	1.10–1.59	0	0	3	42.9	4	57.1	7
Penicillin	1.60 plus	0	0	2	66.7	1	33.3	3
	TOTAL	11	22.0	30	60.0	9	18.0	50
Aureomycin	0 –0.09	3	50.0	3	50.0	0	0	6
Administered	0.10–0.19	5	55.6	4	44.4	0	0	9
Concurrently	0.20–0.39	1	14.3	4	57.1	2	28.6	7
With	0.40–0.69	0	0	9	90.0	1	10.0	10
Penicillin	0.70–1.09	0	0	1	25.0	3	75.0	4
	1.10–1.59	0	0	1	20.0	4	80.0	5
	1.60 plus	0	0	1	50.0	1	50.0	2
	TOTAL	9	20.9	23	53.5	11	25.6	43
GRAND TOTAL		20	21.2	53	57.6	20	21.2	93

* Experiments which showed neither significant antagonism nor significant addition are recorded as showing no effect.

Figure 4 further amplifies the relationship between the drugs and shows that antagonism did not depend so much on the doses or the effectiveness of either drug as it did on the relationship between them. In this chart the significance of the difference between the effect of penicillin and that of aureomycin was tested by the chi square method for each experiment. Only when penicillin was administered in doses sufficient to give significantly greater protection than aureomycin was antagonism observed. In only a few of these experiments was addition present. Whenever the dose of aureomycin was significantly greater either no effect or addition (44.5%) was found. It is important to note that in spite of the high degree of effectiveness of aureomycin, the lesser effect of penicillin was not abolished and in fact showed itself to be present by producing addition. Moreover, whenever the 2 drugs were equally effective, regardless of whether they were both greatly or only slightly effective, marked addition occurred. In the highly effective group this might have been greater than the 60% recorded had it not been for the limitations of the experimental method used.

All of the experiments in which the ratio of survival time of aureomycin to that of penicillin was 0.40 or less have been added together. Among 975 animals receiving penicillin, 514 survived the infection, whereas among 975 receiving the combination treatment, only 416 survived ($x^2=17.0$; $P<.01$). On the other hand, in the experiments with a ratio above 0.40, 276 mice survived among 563 treated with penicillin and 370 survived among 563 treated with the combination ($x^2=32.0$; $P<.01$).

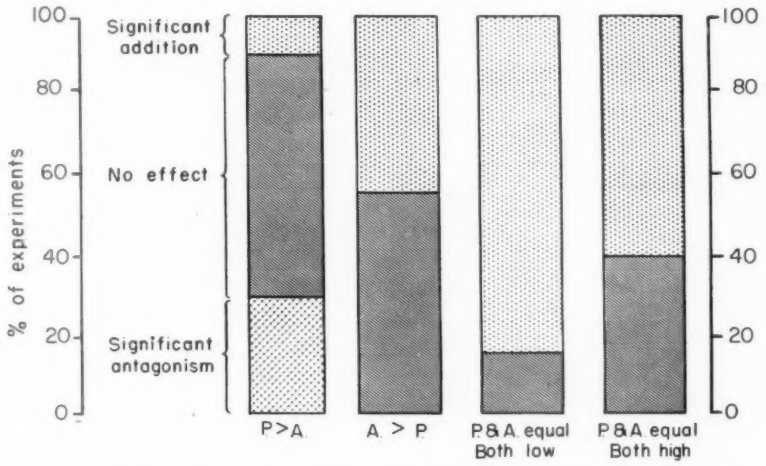

FIG. 4.—Distribution of experiments which showed significant antagonism, significant addition, and no demonstrable effect among 72 experiments where penicillin was significantly more effective than aureomycin, 8 experiments where aureomycin was significantly more effective than penicillin, 7 where penicillin and aureomycin were equally effective but of low order of effectiveness, and 6 where the effect was equal and of high order of effectiveness.

TIME OF TREATMENT. The effect of the time relationship between the administration of aureomycin and penicillin is seen in Figs. 1 to 4. There was no significant difference in the incidence of either addition or antagon-

ism whether aureomycin was administered prior to, or concurrently with, penicillin. However, there was a difference between the 2 groups when one considers the distribution of the experiments showing significant antagonism and, to a lesser extent, those showing addition. Thus when aureomycin was administered 4 hours before penicillin the maximum amount of antagonism occurred at higher aureomycin-penicillin protection ratios than when the 2 drugs were administered together. The same was also true in the case of addition but less markedly so. This may well represent some loss of aureomycin between the time of its administration and that of the penicillin.

In some of the experiments in which aureomycin was administered 4 hours before penicillin, the first antibiotic was given 2 hours after infection and in others, 6 hours. In the experiments where the drugs were administered concurrently they were given just before, 3, 6, and 12 hours after the infection. The interval between the time of infection and the time that treatment was started, within the above limits, had no demonstrable relationship to the incidence of addition or antagonism.

In the 19 experiments in which penicillin administration preceded aureomycin injection by 4 hours, addition occurred in 12 and neither addition nor antagonism in 7. Antagonism was not observed in any of the experiments in spite of the fact that the doses used were often within the range where antagonism had been observed in the experiments in which aureomycin had been given prior to or concomitant with penicillin.

Among the 9 experiments in which the drugs were given every 4 hours there were three showing addition and one antagonism. On the other hand, among the 11 experiments where only a single dose of aureomycin was used, 3 showed addition and 4 antagonism. Since, in these experiments, the doses of the drugs bore the same relationship to the frequency of addition or antagonism as in the entire series of experiments it appears that the treatment schedule was not so closely related to the occurrence of antagonism or addition as the doses of the drugs.

Discussion. Jawetz and his associates[8] demonstrated that a combination of aureomycin and penicillin was sometimes superior in effectiveness to similar doses of penicillin used alone and under other circumstances less effective. We[6] have shown that this is also true in pneumococcic infection in mice.

Ahern and his associates[2] suggested that the phenomenon of antagonism might not take place when multiple doses of the 2 drugs were used, since they did not observe it in mice infected with streptococci and treated with chloramphenicol and penicillin. The experiments reported in the present paper seem to establish the fact that, when mice infected with pneumococci are treated with multiple doses of aureomycin or penicillin or a combination of the two, the combination may be either more effective or less effective than penicillin alone. Furthermore, whether antagonism or addition is observed in a given experiment depends upon the relationship of the doses, or more precisely upon the relationship of the therapeutic effectiveness of the 2 antibiotics. These results are quite similar to those reported by Speck *et al*[10]. It appears likely that Ahern and his associates might have been able to demonstrate the phenomenon of antagonism if they had explored a wide variety of dosage ranges.

That the time relationship between the drugs was of little importance until penicillin preceded aureomycin is of interest. Because of the small number of experiments, one cannot state categorically that antagonism will never occur if penicillin precedes aureomycin by 4 hours or more. However, it is definitely more difficult to demonstrate it, if it exists at all.

Little can be surmised about the mechanism of the antagonism. It occurred only with ineffective doses of aureomycin when the dose of penicillin was effective and *not* with ineffective doses of aureomycin when the dose of penicillin was equally ineffective. Such results might be expected if the larger doses of penicillin were acting by more than one mechanism. Aureomycin blockade of one of these mechanisms without blockade of the other might then be hypothesized to explain the phenomenon. However, an effective dose of aureomycin supplemented either high or low doses of penicillin. One explanation might be that a low dose of aureomycin stimulated an alternate metabolic pathway in the bacterium, by-passing the mechanism affected by a high penicillin concentration while large doses of aureomycin blocked this alternative route.

It is impossible to state the exact clinical significance of the antagonism demonstrated here and elsewhere. The fact that the phenomenon occurs in a restricted range of doses, although it is at the same time demonstrable under a variety of *in vitro* conditions and in animal experiments, would indicate that it has potential clinical significance. This may be the explanation for the results we[9] have obtained in pneumococcic meningitis with combination therapy. On the other hand, addition is somewhat easier to demonstrate and occurs over a wider range than antagonism. Clinical results in some patients with staphylococcic[11] or streptococcic endocarditis suggest that penicillin plus aureomycin or chloramphenicol may have been successful when either penicillin or the broad spectrum drug alone was unsuccessful. In many infections, however, the degree of addition is not so great that more will be accomplished than by raising the dose of the single antibiotic.

In general, we feel that a single antibiotic can be used as successfully as any combination in most infections and that the former is preferable from the point of view of simplicity and toxicity. In some diseases, such as brucellosis[4], tuberculosis[5] and enterococcic endocarditis[3], certain combinations are well established while in other infections more study is needed. If combinations are to be tried in certain fulminating infections on an empirical basis, it would seem wise to use two relatively bactericidal drugs from the group which includes penicillin, streptomycin and bacitracin[7]. On the other hand, there may well be some infections in which the most promising combinations are composed of a bacteriostatic drug such as aureomycin, chloramphenicol or terramycin along with a bactericidal one. When these combinations are tried the maximum practicable doses of each should be employed.

Summary. 1. In 112 experiments mice infected with pneumococci have been treated with aureomycin plus penicillin over a period of 2 to 3 days and the results compared with those obtained by either drug alone.

2. In 50 experiments in which the first dose of aureomycin was given 4 hours before the first dose of penicillin, significant antagonism of penicillin by aureomycin was observed in 11. The 2 drugs showed an additive

effect in 9 experiments. Both effects were observable when the drugs were given on a 4-hour schedule as well as on a 24-hour schedule. A single dose of aureomycin preceding multiple doses of penicillin likewise produced antagonism in some experiments and addition in others.

3. In 43 experiments in which the 2 drugs were administered concurrently, antagonism was present in 9 and addition in 11. Both effects were demonstrated when the drugs were administered just before infection or any time up to and including 12 hours after infection.

4. In 19 experiments where penicillin administration preceded aureomycin by 4 hours, there was no antagonism shown but addition occurred in 12.

5. Antagonism was most likely to occur when the dose of aureomycin was in the low, poorly effective range and when the dose of penicillin was in the highly effective, although not completely protective range. When the ratio of the doses or therapeutic effectiveness of the 2 drugs was calculated, it was possible to find a range of such ratios in which only antagonism or only addition occurred.

6. The clinical implications of these experiments have been discussed.

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FIVE-YEAR FOLLOW-UP OF 100 CASES OF MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN

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Advances in the treatment of miliary and meningeal tuberculosis by antibiotics and chemotherapeutic agents are reflected in an increasing survival of patients treated by each successive regimen. The measurement of survival in the first large group of such patients treated with streptomycin alone warrants recording for comparison with the rather hopeless pre-streptomycin era and as a reference point to demonstrate each increment of survival produced by new chemotherapeutic agents and the combination of various agents.

This report presents the final survival figures for 100 cases of acute disseminated miliary tuberculosis and tuberculous meningitis treated in Veterans Administration Hospitals during one year beginning in April, 1946. These cases, of whom 40 survived 4 to 14.3 months following the initiation of treatment were reported in detail by Bunn[2] as of October, 1947.

The composition of the group and the average daily intra-muscular doses, duration and total of intrathecal therapy were as follows: 22 patients with acute disseminated miliary tuberculosis without meningitis received 2.3 gm. of streptomycin daily for 16 weeks; 10 patients developed tuberculous meningitis during or after similar therapy for miliary tuberculosis and received 2.7 gm. of streptomycin daily for 20 weeks plus 7.1 gm. of streptomycin intrathecally; 25 patients with both miliary and meningeal tuberculosis at the beginning of therapy received 2.3 gm. of streptomycin daily for 11.3 weeks plus 4.6 gm. of streptomycin intrathecally. Forty-three patients with tuberculous meningitis received 2.6 gm. of streptomycin daily for 13.8 weeks plus 6.4 gm. of streptomycin intrathecally. A very large majority of the patients received 1.8 gm. of daily intramuscular streptomycin and 0.1 gm. of streptomycin in each intrathecal injection.

By May, 1949, there remained 21 survivors who had been observed 2 years after completion of treatment and their follow-up was also reported by Bunn[3]. In that report 3 of the patients with miliary tuberculosis were reclassified because of the subsequent development of tuberculous meningitis. In order to extend the follow-up of these patients to 5 years the status of each of the 21 survivors was determined as of May, 1952, and the changes in status between the second and fifth years of follow-up are shown in Table 1.

Interim Status of Survivors Between Second and Fifth Year Post-Treatment. *The Living:* One patient with miliary tuberculosis redisseminated in January, 1952, 4 years after hospital discharge and was rehospitalized on May 19, 1952. Another patient has remained in hospital continuously because of active pulmonary tuberculosis. Two patients had active bone and joint tuberculosis during the past

3 years, were treated with streptomycin and surgery, and are now in good health. Another patient had genitourinary tuberculosis, received streptomycin and, following the removal of an active tuberculous focus in the epididymis, is now apparently well. These last 3 patients and the remaining 4 patients, a total of 7, are not only living but are also well 5 years after treatment of miliary tuberculosis.

One patient treated for miliary and meningeal tuberculosis remains alive and well 5 years later.

Five of the patients with tuberculous meningitis remain alive 5 years after treatment. One patient had recurrent meningitis in 1950, responded to retreatment, but has residual paraplegia of the lower extremities and an impaired mental status. Another patient has, as his only residuals, blindness in one eye and slight weakness of one leg as reported by Aquilina[1]. Three patients have no clear cut residuals of their previous tuberculous meningitis.

The Dead: Two patients treated for miliary tuberculosis and surviving for 2 years died thereafter. One had a reexacerbation of his disease and died in 1949, and another died in 1949 due to the reactivation of pulmonary tuberculosis.

One patient with combined miliary and meningeal tuberculosis was moribund at the time of the 2-year follow-up and died in 1948.

One patient with tuberculous meningitis was moribund when reviewed for the 2-year follow-up and died in 1949. Two patients treated for tuberculous meningitis were considered cured and died of other diseases, one from a massive hemothorax following lobectomy in 1952, the other from nontuberculous disease in 1951.

No patient in this group died of his original miliary or meningeal tuberculosis in 1950, 1951, or early 1952. In other words, all deaths due to the primary disease occurred in the first 2½ years after completion of treatment.

Table 2 shows the 5-year survival compared to the 2-year survival[3] and to the initial series[2]. Since this series of cases reached a state of equilibrium in terms of survival from miliary tuberculosis and tuberculous meningitis at the 2½-year post-treatment level (there being no deaths due to the original disease in the last 2½ years) the final survival status is presented in Table 3, which omits deaths due to other causes.

TABLE 1.—INTERIM STATUS OF 21 SURVIVORS OF MILIARY AND MENINGEAL TUBERCULOSIS (2ND TO 5TH YEAR OF FOLLOW-UP)

	Surviving at 2 years	*Living at 5 years*	*Died 2–5 years*
Miliary	11	9(a)	2(b)
Miliary followed by meningitis	0	0	0
Miliary and meningitis combined	2	1	1(c)
Meningitis	8	5	3(d)
	21	15	6

(a) 1 showed signs of redissemination 5/12/52
(b) 1 died of miliary tuberculosis on 6/29/49
1 died of reactivation of pulmonary tuberculosis 9/26/49
(c) Moribund on 1950 report[3]
(d) 1 was moribund on 1950 report[3]
1 surgical death, not related to meningitis
1 non-tuberculous death

As is evident from the table, 9 of the 19 cases (47%) of acute disseminated miliary tuberculosis treated with streptomycin recovered from the original disease. Of these, one patient redisseminated at the end of 5 years and one remains in hospital with active pulmonary tuberculosis. Seven patients were fully recovered and well at the time of the 5-year follow-up.

TABLE 2.—SURVIVAL OF 100 CASES OF MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN (2 AND 5-YEAR FOLLOW-UP)

		1st Report[2](a)		*2-year follow-up*[3]		*5-year follow-up*	
	Total	*Living*	*%*	*Living*	*%*	*Living*	*%*
Miliary	22(19)*	16	73	11	58	9	47
Miliary followed by meningitis	10(13)*	3	30	0	0	0	0
Miliary and meningitis combined	25	5	20	2	8	1	4
Meningitis	43	16	37	8	18	5	12
	100	40	40	21	21	15	15

(a) Survivors 4 to 14.3 months after start of therapy

* Reclassification at second report because 3 cases of miliary tuberculosis developed tuberculous meningitis

TABLE 3.—SURVIVAL OF 100 CASES OF MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN (2½-YEAR FOLLOW-UP)

	Total	*Living*	*%*
Miliary	19	9	47
Miliary followed by meningitis	13	0	0
Miliary and meningitis combined	25	1	4
Meningitis	43	7	16
	100	17	17

None of the 13 cases of miliary tuberculosis followed by meningitis was living 2 years after treatment, while one of the 25 cases (4%) of miliary and meningeal tuberculosis combined recovered and was well 5 years later.

Seven of the 43 cases (16%) of tuberculous meningitis recovered and were alive 2½ years after treatment though 2 patients did not live to the 5-year point because of factors not directly related to meningeal tuberculosis. Of the 5 patients (12%) living at the 5-year follow-up, only 3 patients (7%) were well and without significant residuals.

Summary. 1. Of 100 cases of miliary and meningeal tuberculosis treated with streptomycin in the 13 months subsequent to April 1946 in 47 Veterans Administration Hospitals, the percentages alive and well 5 years later were as follows:

a. Miliary tuberculosis, alive 47%, and well 37%.
b. Miliary tuberculosis followed by tuberculous meningitis, alive 0%.
c. Miliary tuberculosis and tuberculous meningitis combined, alive and well 4%.
d. Tuberculous meningitis, alive 12%, and well 7%.

2. All deaths due to the original disease occurred in the first 2½ years after termination of treatment.

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EPIDEMIC HEMORRHAGIC FEVER

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Hemorrhagic fever is a new and strange disease which our Armed Forces in the Far East have encountered during the Korean conflict. This entity with its long incubation period is of interest to both the civilian and military physician in the United States, as either may see it in the returning servicemen. Hemorrhagic fever is an acute infectious disease first seen by our military physicians in the early summer of 1951. It is presumably of virus etiology and transmitted by bite of the mite or tick, characterized by an abrupt onset with upper respiratory infection-like symptoms, high fever, postorbital headache, myalgia, hemorrhagic diathesis, shock, oliguria with albuminuria and leukemoid leukocytosis.

Historical. The disease has been known to exist from time immemorial as a type of occupational disease in the Russo-Manchurian regions, according to information obtained from native Manchurians and old physicians of the Chinese practice of medicine. Acute hemorrhagic fever was recognized as a clinical entity in 1934 when the Russians called it "Churilov's disease." The Japanese, in 1936, also recognized this disease as a new malady. The military troop movements of Russia and Japan with their progressive occupation of infected localities in Manchuria and adjacent areas in Siberia precipitated an alarming increase in the number of outbreaks of acute hemorrhagic fever. This disease was observed mostly in semi-rural or chiefly rural surroundings, among people living in the open, in tents, or in recent settlements of agricultural immigrants, in military camps and among others whose occupation involved handling of hay and fodder. It is endemic in the shrubby, marshy, swampy regions along rivers of Northeastern Manchuria and adjacent Siberia, and also may occur in entirely isolated districts[3]. There are some who believe that native Manchurians are rarely affected by the epidemics.

The Japanese reports show that the disease was common between years 1936 and 1942 in troops stationed in the northeastern provinces of Manchuria. The epidemic outbreaks remained localized, involving certain companies and regiments, with the number of soldiers afflicted remaining small. Sometimes as many as 10% of the troops became sick, while the incidence in epidemics usually was 1%. The mortality rate varied from year to year, from district to district, and from season to season. The Japanese estimated the mortality rate at 16%. The seasonal incidence occurs twice each year, once in the spring (April, May) and again in the early fall (September, October), coinciding with the periods when the multiplication of the mite is at its height[4]. Near the 50th parallel, the disease appears epidemically one month later, namely, May and June,

and October and November, but occurs sporadically throughout the year. The Russians made similar observations as to the average size and time and number of epidemics.

ETIOLOGY. The Japanese and Russian physicians in their studies of the disease claimed that the pathologic organism was a filterable virus and not a bacterial or rickettsial disease, although a few Japanese consider it to be a rickettsial disease. Emulsions prepared from virus-containing material or from infected Laelaps mites were reported to cause typical specific disease in monkeys and man. This work has not been verified by United States research physicians innoculating the common laboratory animals useful in transmission of virus and rickettsial diseases, including monkeys imported from the Philippines. It is still considered likely that the causative organism is a filter-passing agent with extremely fastidious growth requirements. To the military and civilian scientists the etiological agent of this disease remains a mystery.

EPIDEMIOLOGY. In May, 1951, epidemic hemorrhagic fever appeared in the United Nations troops just north of the 38th parallel and near Yonchon, Korea, in areas recently evacuated by the Chinese and North Korean troops. Cases appeared in a few companies in regiments occupying the valleys and not in other units (Fig. 1). The peak incidence occurred as noted in Japanese and Russian reports in May, June, July and in the fall (October and November) with the former months producing higher mortality rates. No secondary cases occurred among the United Nations doctors, nurses, attendants and research workers, indicating no person-to-person transmission. With such a regional disease, the transmitting agent must be insect borne, such as mite or tick. The infection is reported to be acquired by the bite of the mite (Laelaps) from the Manchurian field mouse, a possible animal reservoir, usually without the victim being aware he was bitten. This is in contrast to scrub typhus, a disease seen in Manchuria, which is transmitted by the mite Trombicula, producing a marked eschar at the site of the bite. A very recent report from Korea states that the Laelaps mite infests rodents and other animals in Korea.

Figures on morbidity rates cannot be given here, but the disease has not presented a major problem in this regard. Mortality from the disease has varied considerably in earlier reports. Mayer[3] cites figures ranging from 3 to 31.8%. His mortality figure for cases occurring in United Nations Troops in Korea during 1950 and 1951 is 13.3%. Data available for U.S. Army personnel in Korea show case fatality rates as follows: Spring-summer phase (April-August) 1951, 14.6%; fall-winter phase (September - March) 1951 - 52, 5.7% spring-summer phase 1952, 5.1%; fall-winter phase, 1952-53 (through January 1953, only), 2.7%. It is not clear to what extent this improvement in the fatality rate reflects improved treatment or better recognition of the milder cases. However, it is believed that for the spring-summer phase of the disease in 1951, there was considerable under-reporting, particularly of the less serious cases.

It is of some interest that the incidence so far this autumn has been considerably lower than that of the same period last year. This may be due to application of mite control measures such as burning grasses, rodent control and impregnation of clothing with miticides.

PATHOLOGY. The basic pathologic lesion in epidemic hemorrhagic fever appears to be a diffuse capillary damage (widespread non-inflammatory disorder of capillary circulation) with capillary dilation, increased capillary

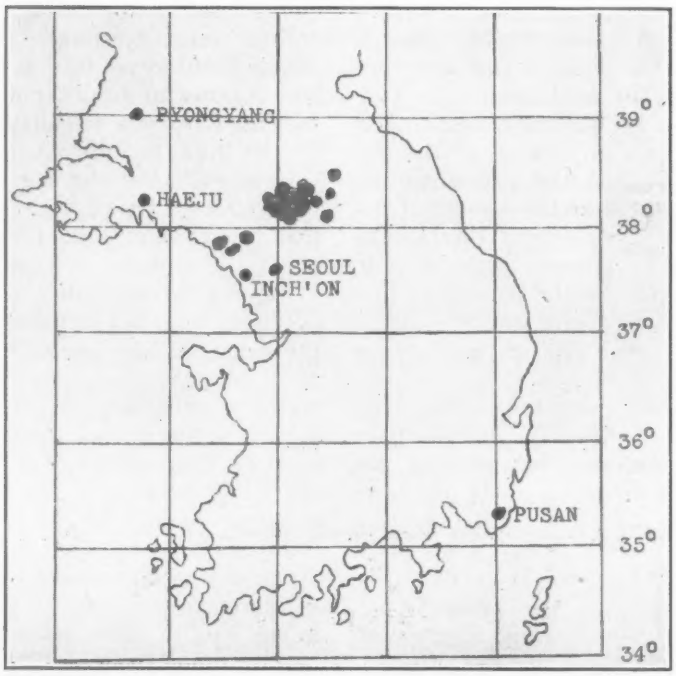

FIG. 1.—Spot Map of Endemic Area in Korea of Epidemic Hemorrhagic Fever.

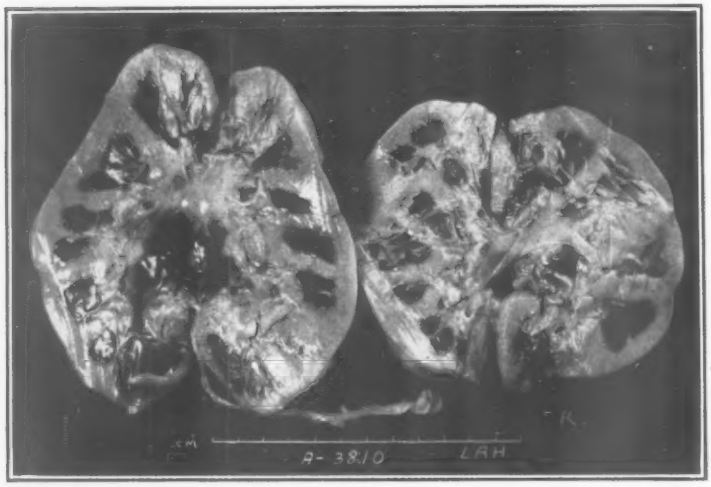

FIG. 2.—Epidemic Hemorrhagic Fever: Sagittal Section of Kidney.

fragility and permeability of the vascular system with hyperemia and small or large purpuric or ecchymotic hemorrhages, often with free bleeding or oozing of blood on the surface. This produces a marked diffuse disturbance in the peripheral circulation with hemoconcentration, hypotension, and inadequate circulating blood volume.

The kidneys present the most characteristic lesions of the disease. These organs are large and swollen and the cut surface reveals a striking contrast between cortex and medulla (Fig. 2). The cortex is pale, with petechiae and focal congestion, while the pyramids are dark cherry-red and hemorrhagic. The renal tubes are often filled with extravasated blood and show necrosis. There is parenchymatous degeneration of a diffuse type throughout the kidney as seen in nephrosis.

The other typical lesion is seen in the anterior lobe of the pituitary. Here the hemorrhagic tendency is so great in 75% that the gland resembles a hematoma and may weigh 2 gm. The anterior lobe shows the greater involvement revealing congestion, necroses and hemorrhage (Fig. 3). The heart is dilated and soft with a relatively common finding of hemorrhage into the wall of the right atrium. There may be focal necrosis in the myocardium, endocardium and epicardium, with or without hemorrhage.

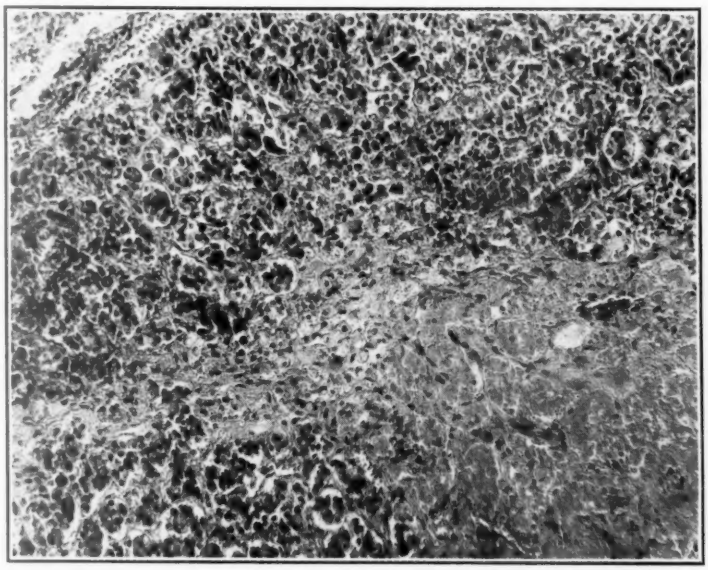

FIG. 3.—Epidemic Hemorrhagic Fever: Photomicrograph of Anterior Lobe Pituitary Gland.

There are three general morphological abnormalities seen microscopically[1]: (1) focal necrosis suggesting infarction, seen in decreasing order of frequency in kidney, pituitary, adrenal, pancreas and liver; (2) marked engorgement, increased permeability and rupture of capillaries, and (3) an inflammatory reaction, consisting chiefly of proliferation of tissue and macrophages and infiltration of immature leukocytes. It is remarkable that areas of hemorrhage and necrosis do not appear to be the prime excitants of this reaction.

SYMPTOMATOLOGY. The incubation period is usually from 2 to 3 weeks but may vary from 7 to 35 or more days. Human experiments of the Japanese and Russians fix the incubation period at 12 to 24 days. The United Nations' incubation data are based on deduction, inasmuch as the etiology has not been determined. Individuals were observed to develop the disease in varying periods upon rotation from Japan.

The onset may be either insidious or abrupt, varying greatly in its severity, but the majority of cases follow a fairly typical course. The prodromes last for a day or two, with upper respiratory symptoms such as nasal congestion, flushed face, dry hacking cough, sore throat, general malaise and occasionally diarrhea. Then the disease is ushered in abruptly by chills, fever and signs of general toxicity. There is a rapidly rising fever of 100° F. to 104° F., even to as high as 106° F., remaining so for 3 or 4 days and then gradually returning to normal about the seventh day. Initially a bradycardia is observed with the fever. Other features at onset include a severe headache, frequently retro-orbital, and an altered appearance of the skin of face, neck and upper chest, which looks deeply flushed or sunburned. There generally is slight edema about the face and periorbital tissue with injection of the conjunctiva. At this time the patient appears listless, stares straight up or perhaps has his eyes closed, and complains of blurred vision, photophobia and diplopia. He says that any movement of his eyes is painful and if he could scratch behind them it would help tremendously. Restlessness, weakness, myalgia and lumbar pain are prominent symptoms. Anorexia appears early with the development of nausea and vomiting on the third or fourth day of illness. Thirst is great and may lead to excessive fluid intake.

Hemorrhagic manifestations begin after the third or fourth day of the disease. Small petechiae appear in the conjunctiva and sclerae and may coalesce into ecchymoses and subscleral hemorrhages. Elsewhere hemorrhagic manifestations appear, especially from mucous membranes and gums. Epistaxis sometimes is difficult to control. As the bleeding tendency develops, one may see hematemesis, hemoptysis, hematuria and bloody diarrhea. Meningismus occurs, which might be produced by subarachnoid hemorrhage. The skin has small petechiae. Ecchymoses appear at sites of trauma. A single injection of medication, a tourniquet or blood pressure cuff may cause ecchymosis of an entire extremity (Fig. 4). A traumatic hemorrhage makes its appearance wherever the clothing is constricting, such as axilla or belt line. As would be expected, the Rumpel-Leede phenomenon is positive. Palpation of the abdomen must be gently performed; a ruptured spleen has been found at necropsy. The hemorrhagic manifestations reach a maximum on the tenth day and then gradually disappear.

As the temperature returns toward normal level, hypotension is seen and in 30% of cases progress into shock. This appears usually at the end of the first week and lasts from a few hours to 3 days or more. Shock is ushered in by apprehension, restlessness and sometimes diaphoresis. It is due to extensive capillary damage. A fall in blood pressure and rising pulse rate with a weak thready pulse are characteristic. In severe cases the blood pressure and peripheral pulse are unobtainable, neck veins collapse, and heart sounds are weak and rapid, with apical rate of 150 per minute or more. Dyspnea and cyanosis accompany the hypotensive state. Abdominal pain may

be severe, frequently periumbilical in location and generally aggravated by fluid intake. In non-fatal cases these changes regress.

The urinary output decreases at the onset of disease but only reaches the oliguria phase when the fever subsides. The oliguria can progress to anuria from which the patient may or may not recover. The symptoms of acute azotemia appear. Vomiting may now be a problem along with exhausting hiccough, abdominal pain and backache. The patient is tense, combative and irritable, complaining of insomnia and nightmares. Neuromuscular hyperexcitability is present and may progress to tetany. In some cases uremic frost, pericarditis, diarrhea and the weakness of hyperkalemia occur. At this time a mild, but rarely severe hypertension may be seen (Table 1).

The oliguria terminates in a profuse diuresis, usually near the tenth day of illness, accompanied by a striking subsidence of the subjective and objective manifestations. In the majority, the recovery is quite dramatic. The appetite returns. Strength and weight are regained. The urine is dilute and profuse. The inability of the kidney to concentrate urine continues for 4 to 6 weeks, rarely longer. The length of convalescence is in proportion to the severity and duration of the renal involvement. When the functional capacity of the kidney is restored to normal, convalescence is complete.

Laboratory Data. *Urine.* Albuminuria appears within the first 48 to 72 hours. During the febrile phase the urinary volume is scanty and the specific gravity varies from 1.025 to 1.032.

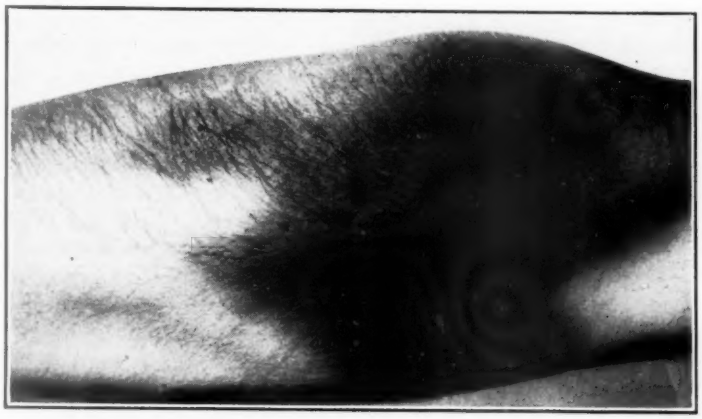

Fig. 4.—Epidemic Hemorrhagic Fever: Ecchymosis of Skin—Elbow.

In early convalescence the urine is very dilute, with a specific gravity varying from 1.002 to 1.006. Commonly seen as a feature of the hemorrhagic phenomenon is microscopic hematuria, appearing early, with gross hematuria later. Granular, waxy and red blood cell casts appear early and disappear with clinical improvement. The concentrating ability of the kidney is lost for 4 to 8 weeks.

Hematology. The blood picture varies with the course of the disease. At the onset of symptoms a normal white blood cell count or a leukopenia is present, followed in 3 to 4 days by a rapidly rising leukocyte count, with

TABLE 1.—CLINICAL FINDINGS IN EPIDEMIC HEMORRHAGIC FEVER

Toxicity with high fever	100%	Hemorrhagic manifestations	86%
Chills	97%	Petechiae, conjunctivae	86%
Bradycardia	93%	Epistaxis	42%
Nausea and vomiting	91%	Bleeding gums	38%
Headache	91%	Traumatic ecchymosis	32%
Eye involvement	100%	Hemoptysis	16%
Injected conjunctivae	91%	Hematemesis	24%
Retro-bulbar pain	90%	Melena and diarrhea	19%
Photophobia	48%	Rumpel-Leede	Positive
Pain on ocular motion	47%	Lower nephron nephrosis	60%
Blurred vision	40%	Oliguria	60%
Flushed or dusky skin—neck and face	88%	Polyuria	60%
Abdominal pain and tenderness	84%	Polydypsia	53%
Backache and myalgia	86%	Restlessness, irrational, convulsions	38%
Periorbital edema	76%	Dyspnea and cyanosis	18%
Sore throat, injected pharynx and cough	68%	Hepato- and splenomegaly	3%

TABLE 2.—PERIPHERAL BLOOD FINDINGS IN COURSE OF EPIDEMIC HEMORRHAGIC FEVER*

1st–3rd Day	*4th–10th Day*	*12th–21st Day*
	LEUKOCYTES	
Normal	Increased—15,000–100,000	Normal
	GRANULOCYTES	
Normal	Immature neutrophiles Few promyelocytes or Leukemoid reaction	Normal
	ERYTHROCYTES	
Normal	Occasional normoblast 1–2:100 WBC	Normal
	EOSINOPHILES	
Normal	Variable 0–8%	Freq. Inc to 8%
	LYMPHOCYTES	
Normal	Atypical lymphocytes 5–25%. Occasional plasma cell. Türk cells	Normal
	MONOCYTES	
Normal	Variable. Occas. increase 10–12%. Atypical forms. Phagocytosis	May be increased to 10–14%
	PLATELETS	
Normal	Decreased—5,000–150,000	Normal. May be high; up to 500,000 between 10–14 days

* As modified from unpublished data of Col. G. M. Powell, Chief, Medicine, Osaka Army Hospital

an average of 20,000 to 40,000 per c.mm. and occasionally as high as 100,000. In serious cases there is an extereme shift to the left, with the appearance of metamyelocytes and myelocytes, Türk irritation cells, and a leukemoid blood picture. On the fifth or sixth day the lymphocyte count rises and many atypical lymphocytes are seen. Failure of these lymphocytes to appear probably indicates a poor immune response and a grave prognosis. During convalescence the leukocyte count returns promptly to normal. Platelets may fall to about 100,000 per c.mm. in the first week and in severe disease may be lower (Table 2).

As would be expected, the Rumpel-Leede test is positive as an indication of the increased capillary fragility. There is also prolonged bleeding time, while the coagulation time and prothrombin time are likely to be within normal range. With the oliguria one sees the usually accompanying azotemia, with blood urea nitrogen up to 60 or 80 mg. per 100 cc. and even higher. This finding disappears as the kidneys regain their functioning ability. The oliguria and azotemia produce hyperpotassemia, hypercalcemia and hyperphosphatemia. The hyperpotassemia is reflected in the electrocardiogram. Hypochloremia is seen only in uncontrolled vomiting. Other chemical analyses and function tests show no significant abnormality.

DIAGNOSIS. At present there is no diagnostic test for this disease. Diagnosis is, therefore, based on a history of residence in Korea, the clinical course and the laboratory findings. The principal clinical features are the abrupt onset in a toxic appearing individual with injected conjunctivae, retrobulbar headache and albuminuria.

The diseases common to Korea which may be confused with acute hemorrhagic fever are epidemic typhus fever, the purpuras, meningococcemia, hemorrhagic smallpox, hemophilia, subacute bacterial endocarditis, relapsing fever, acute leukemia, leptospirosis, acute glomerulonephritis, and drug or chemical poisoning.

TREATMENT. At the present time there is no effective therapeutic agent for acute hemorrhagic fever. Management is based on careful fluid restriction, bed rest and sedation. Prompt hospitalization with complete bed rest and adequate sedation with barbiturates and Demerol lessen bleeding, vomiting, shock and morbidity. Patients with high fever of 105° F. or 106° F. are treated with acetylsalicylic acid and cold sponge baths. Convalescent whole blood in amounts of 250 to 300 cc. or serum may be beneficial when given during the first days of illness. When these patients were first seen in the summer of 1951 it was noted that the administration of a mere 1 or 2 liters of isotonic saline could precipitate a fatal pulmonary edema. Fluids are to be given cautiously and only in quantities sufficient to maintain electrolyte balance and not in the usual amount customarily administered in acute toxic states. Overhydration increases abdominal pain, may produce excessive edema aggravating shock and, with cardiac damage present, may lead to failure.

All measures that normally would be expected to be effective have been disappointing. No single agent has had any dramatic effect on the course of the disease. In fact, antibiotics, corticotropin (ACTH), cortisone, a variety of agents used in the hemorrhagic diatheses and many other empirically used drugs have failed to have any significant effect. Antibiotics may be used to prevent suspected invasion of other diseases.

Management of the shock or hypotensive state is directed toward maintaining an effective blood pressure without overhydrating the patient un-

til the cardiovascular system integrity is restored. This is based on the early control of fluid intake as governed by intake and output records. Prophylactic measures in management of early phase will reduce shock manifestations to a minimum. Certain adjuncts which have proven somewhat effective in support of blood pressure and pulse pressure are the use of the Trendelenburg position, elastic bandages on legs and thighs, pressor amines (epinephine or ephedrine and norepinephrine), whole blood, plasma and concentrated human albumin. After continuous usage these agents lose their effectiveness[2].

No effective therapeutic agent has been found to be beneficial in the management of the hemorrhagic manifestations of the disease. Trauma is the most important precipitating factor in ecchymosis, hence, parenteral injections and tight clothing are to be avoided. Restlessness, coughing, vomiting, combativeness and straining, if not adequately controlled with sedation, may lead to further hemorrhage.

The course of the renal involvement is similar to that of lower nephron nephrosis, and treatment is based on the use of adequate fluid and electrolyte management. With return of complete renal functioning ability, the soldier is released from convalescent care and returned to his military duties.

Summary. Epidemic hemorrhagic fever is a specific regional, endemic disease with semiannual (spring and fall) outbreaks, occurring in Northeastern Manchuria and adjacent areas of Siberia and Korea, of unknown etiology but presumably virus transmitted by mites (Laelaps) from rodents. There is no evidence of infection person-to-person. The mortality rate in cases occurring in United States Army troops in the spring-summer phase in 1952 was 5.1% and in the fall-winter phase in 1952-53 was only about 2.7%.

The basic pathologic lesion is a diffuse capillary toxicity and focal necrosis suggesting infarction. The characteristic lesions are seen in kidneys and pituitary, with hemorrhage into renal medulla and anterior lobe of pituitary. Hemorrhage and ecchymosis appear in skin, mucous membrane and conjunctivae.

The disease is ushered in abruptly by chills, fever and general toxicity for 5 to 7 days. Retro-orbital headache, injection of conjunctivae and bradycardia are almost always present. Then follow mild to severe shock, hemorrhagic diathesis, renal insufficiency, terminating fatally or in complete convalescence. A pronounced leukocytosis and decreased platelet count are present, with urinary findings consistent with lower nephron nephrosis.

Hemorrhagic fever has no specific effective therapeutic agent. The usual supportive measures are practiced. Therapy is directed toward avoiding overhydration, maintenance of electrolyte balance, avoidance of trauma and treatment of shock. All available antimicrobial agents and many other drugs have no clinical benefits.

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RENAL CALCULI AND UREMIA AS COMPLICATIONS OF LYMPHOMA

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The renal complications of lymphoma due to direct parenchymal or perirenal involvement are commonly appreciated[9]. The purpose of this report is to emphasize another type of renal complication of lymphomas which occurs with greater frequency than has been generally recognized. This complication is renal calculus formation which may occasionally be sufficiently severe to cause renal obstruction, uremia and death.

Elevation of serum uric acid and increased urinary excretion of uric acid is known to occur in leukemia and related diseases. Since uric acid is one of the chief end products of purine catabolism, increased formation of uric acid occurs whenever excessive breakdown of nucleoproteins takes place[14]. With the advent of potent therapeutic agents capable of producing rapid and extensive nuclear destruction, there have been occasional reports of uremia following therapy in patients with lymphoma. In these patients urinary obstruction resulted from the precipitation of urates and uric acid in the collecting tubules or ureters. Fifteen such cases of uremia have been reported thus far[1,6-8,10,11]. Thirteen have been in patients with leukemia and one was in a patient in whom the clinical findings were those of acute lymphatic leukemia although the pathologic diagnosis was Hodgkin's sarcoma[11]. Only one case of uremia has been reported in a patient with lymphosarcoma[7]. The occurrence within a short period of time of 2 fatal cases of uremia due to uric acid deposits in patients with lymphomas other than leukemia has prompted us to investigate this problem further. In addition, although uric acid calculi are known to occur frequently in patients with

TABLE 1.—INCIDENCE OF URIC ACID CALCULI ACCORDING TO DIAGNOSIS

	Number of Cases	*Incidence*
Acute Leukemia	68	3
Chronic Myeloid Leukemia	69	3
Chronic Lymphoid Leukemia	52	3
Total	189	9 (4.76%)
Hodgkin's	47	0
Lymphosarcoma	34	3
Reticulum-cell Sarcoma	4	1
Giant Follicular Lymphoblastoma	5	1
Agnogenic Myeloid Metaplasia	4	1
Total	94	6 (6.38%)

lymphoma, we have been unable to find a study of the incidence of this complication in a large series.

Material and Results. The incidence of renal calculi was determined by examining the records of all adult patients with lymphomas who had been admitted to the University Hospitals of Cleveland within the past 10 years (Table 1). Included in this survey were patients with diagnoses of acute and chronic leukemia, Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, giant follicular lymphoblastoma and agnogenic myeloid metaplasia. The incidence of renal calculi in this group of patients was compared with the incidence in 100 patients with metastatic malignancies such as breast, lung, gastrointestinal and thyroid chosen at random, who had received radiation therapy.

Fifteen of 283 patients (5.3%) with lymphomas whose records were examined were found to have proven renal calculi. Seven of these were analyzed and found to be uric calculi. No renal calculi were found in the 100 patients with metastatic malignancies other than lymphoma (Table 2). Twelve of the 15 patients in whom renal calculi were diagnosed passed calculi either spontaneously or following cystoscopic intervention. In the remaining 3 patients the presence of renal calculi was demonstrated at postmortem examination.

TABLE 2.—INCIDENCE OF URIC ACID CALCULI

	Cases	*Incidence*	
		No.	*Per cent*
Lymphoma	283	15	5.3
Malignancy	100	0	0.0
General Hospital Population	—	—	0.07

The incidence according to type of lymphoma is shown in Table 1. Nine of 189 patients (4.76%) with leukemia and 6 of 94 patients (6.38%) with other types of lymphoma were found to have renal calculi. No calculi developed in any of the 47 patients with Hodgkin's disease whereas calculi were demonstrated in one or more patients with other types of lymphoma.

Five of the 15 patients who developed renal calculi received no therapy except blood transfusions and antibiotics. The remaining patients received Roentgen-ray therapy, radioactive phosphorus or nitrogen mustard either alone or in various combinations at periodic intervals.

The blood uric acid in patients with renal calculi ranged from 4.0 mg. per 100 cc. to 36.0 mg. per 100 cc. However, the blood uric acid was above 10 mg. per 100 cc. in only 2 of the patients. Because the urinary excretion of uric acid had not been determined in any of the patients with calculi, it was determined in 5 patients with lymphoma without calculi. The excretion of uric acid was markedly increased as has been shown by others[3,4,12]. The maximum output ranged from 965 mg. per 24 hours to 2970 mg. per 24 hours (Table 3) compared with the normal output of 100 to 500 mg. per 24 hours[2]. The daily uric acid output of one of the patients is shown in Fig. 1.

TABLE 3.—MAXIMAL URINE URIC ACID EXCRETION IN PATIENTS WITH LYMPHOMA

Diagnosis	*Total Output (mg./24 hr.)*
Lymphosarcoma	1950
Chronic Lymphatic Leukemia	1270
Chronic Myeloid Leukemia	2970
Lymphosarcoma	1072
Chronic Lymphatic Leukemia	965

The urinary pH in all patients who developed calculi was acid. Acidification of the urine was enhanced by the administration of ammonium chloride

as a diuretic in 4 patients. Pyelonephritis was not present as a precipitating factor but developed in 2 patients after calculus formation took place.

The 2 fatal cases of uremia encountered were in patients with lymphosarcoma and agnogenic myeloid metaplasia. A summary of these cases follows.

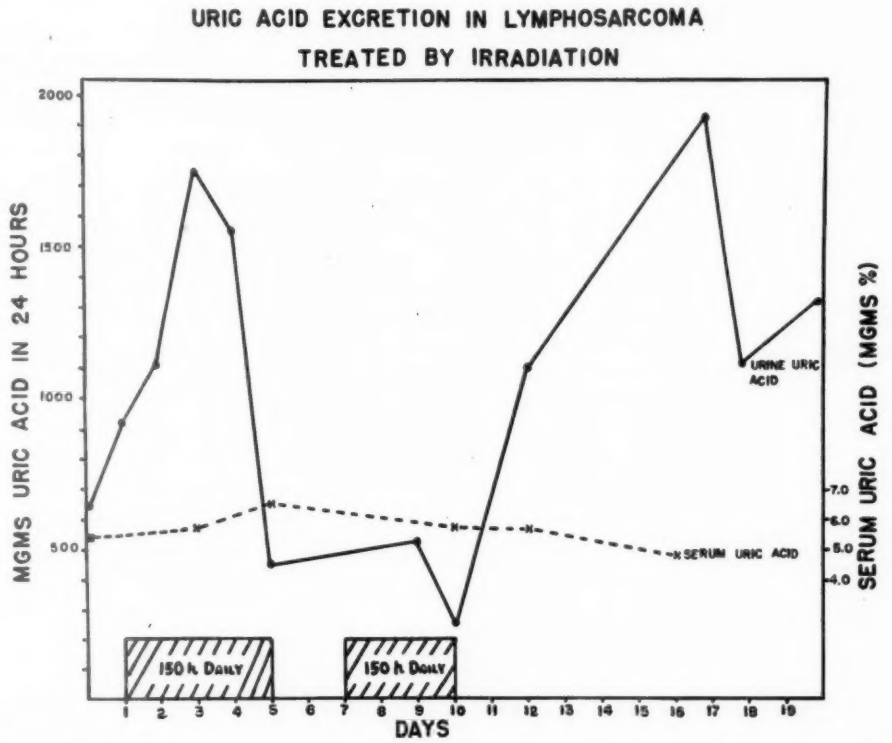

FIG. 1.—Urinary uric acid excretion during and following treatment with Roentgen-ray. Initial high levels were not maintained during therapy, but were regained after cessation of treatment.

Case Reports. CASE NO. 1. F.K., (619-940), a 50-year old white male with proven lymphosarcoma of 7 months' duration was admitted to the University Hospitals for nitrogen mustard therapy after failing to respond to radiation therapy. On admission he had enlargement of the cervical, axillary, inguinal and retroperitoneal nodes as well as enlargement of the liver and spleen. He was given 0.4 mg. of nitrogen mustard per kg. intravenously in a single dose instead of the conventional 0.1 mg. per kg. daily for 4 days. Within 24 hours there was rapid regression and within 3 days complete disappearance of all visible and palpable masses. However, 2 days after the mustard therapy he developed oliguria. Subsequently the blood urea nitrogen rose from a level of 12.0 mg. per 100 cc. to 179 mg. per 100 cc. and the creatinine rose to 8.5 mg. per 100 cc. He died 8 days after institution of therapy. The serum uric acid terminally was 36.0 mg. per 100 cc. On postmortem examination there was widespread deposition of uric acid throughout the collecting tubes of the kidneys. Although there was no gross evidence of lymphosarcoma, on microscopic examination lymphosarcoma infiltrations were present in the kidneys and other organs as well.

CASE NO. 2. R.A. (287-034) was a 38-year old white male who had had known splenomegaly for 11 years. The bone marrow and peripheral blood findings were typical of agnogenic myeloid metaplasia and a lymph

node biopsy showed extramedullary hematopoiesis. At the time of the terminal episode he was in relatively good condition despite extreme enlargement of the liver and spleen and minimal congestive failure which was treated successfully with ammonium chloride and mercurial diuretics. Spontaneous regression in the size of the liver and spleen developed insidiously. Coincident with this he began to pass large numbers of uric acid calculi intermittently for a period of 2 months. During this period he developed gouty arthritis. Ultimately, he developed urinary tract obstruction despite repeated cystoscopic manipulations with removal of large amounts of inspissated gravel. Uremia and septicemia leading to death followed. The serum uric acid rose to 13.8 mg. per 100 cc. terminally. Postmortem examination revealed left pyelonephritis, marked with evidence of obstructive uropathy in addition to the known agnogenic myeloid metaplasia.

Discussion. The occurrence of renal calculi in 5.3% of patients with lymphomas represents a significant increase over the number normally found in hospital patients. The incidence of uric acid calculi in 108,947 general hospital admissions as determined from the data of Kittridge and Downs[5] pertaining to all types of calculi and from the data of Prien[15] concerning the percentages of uric acid stones is 0.07%. Thus the incidence of uric acid calculi in patients with lymphomas is approximately 75 times as great as that in the general hospital population. Even if compared to the incidence of all types of calculi in the general hospital population (1.2%), there is a significantly higher incidence in lymphoma.

The incidence of calculi in non-leukemic patients with lymphoma was slightly higher than the incidence in leukemic patients. However, no calculi developed in any of the 47 patients with Hodgkin's disease. This may be due to the pleomorphic and desmoplastic histologic pattern found in Hodgkin's rather than the hyperproliferation of a single cell type characteristic of the other lymphomas. If Hodgkin's disease were excluded from this series, the incidence in the non-leukemic patients would be significantly greater than the incidence in leukemia. Furthermore, the severity of obstruction appeared to be somewhat greater in the non-leukemic patients. Thus the 2 deaths due to uremia occurred in this group of patients, whereas uremia did not develop in any of the patients with leukemia.

In all cases previously reported in the literature uremia developed following therapy. However, therapy is not necessarily a precipitating factor either in the formation of calculi or in the subsequent development of uremia. Thus renal calculi developed in 5 patients who had received no specific therapy. Uremia, as a sequel to calculus formation, developed spontaneously in Case 2 even though no specific therapy was administered. Intensive therapy may, however, be a factor in calculus formation by causing excessive nucleoprotein breakdown so that the amount of uric acid subsequently excreted exceeds the urinary solubility. Thus the administration of 0.4 mg. of nitrogen mustard per kg. body weight in a single dose to a patient with lymphosarcoma which was evidently extremely sensitive to mustard, resulted in uremia and death (Case 1).

Factors such as preexisting renal impairment, lymphomatous involvement of the renal parenchyma or pyelonephritis may contribute to the development of uremia. However the chief precipitating factor is the deposition of uric acid in the collecting tubules and ureters. The latter occurs whenever the urinary solubility is exceeded, which may readily take place when the urinary volume is not adequate or when the solubility of uric acid is decreased by acidification of the urine. Thus the use of ammonium chloride in the presence of cardiac

failure was associated with renal calculi in 4 patients.

Prophylactic measures should, therefore, include adequate urinary output and alkalinization of the urine. Careful study of renal function prior to instituting therapy should be routine. During therapy the blood uric acid, creatinine, urea nitrogen or non-protein nitrogen should be determined at intervals and frequent examinations of the urinary sediment should be performed. Spacing of therapy may be advisable when there is an extensive mass of hyperproliferating tissue or when there is reason to believe that the lymphoma may be highly sensitive to the therapeutic agent being employed. Local irradiation of the kidneys prior to more extensive irradiation has been suggested as a prophylactic measure if renal parenchymal involvement by the lymphoma is suspected[13]. A low purine diet so as to decrease exogenous uric acid formation has also been suggested[4], and drugs which are known to increase the output of uric acid should be avoided. Cystoscopic manipulation may be lifesaving if ureteral obstruction develops.

Summary and Conclusions. The incidence of renal calculi and uremia in patients with lymphoma is greater than has been generally recognized. Renal calculi were found in 5.3% of 283 hospitalized patients with lymphoma (acute and chronic leukemia, Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, giant follicular lymphoblastoma and agnogenic myeloid metaplasia). No calculi were found in 100 patients with metastatic malignancies of other types who had been treated by irradiation.

The incidence of renal calculi in leukemia as compared to the incidence in non-leukemic patients with lymphoma was determined. With the exception of Hodgkin's disease, the incidence in non-leukemic patients is as great or greater than in leukemic patients. Two cases of uremia in non-leukemic lymphomatous patients are reported.

The renal complications of lymphoma are potentially fatal and frequently avoidable. Prophylactic measures should be routine and should include maintenance of adequate urinary output, alkalinization of the urine and careful evaluation of renal function before and during therapy. Other prophylactic measures are discussed.

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POSSIBLE RELATIONSHIP OF FOLIC ACID TO URIC ACID METABOLISM AS EXEMPLIFIED BY A CASE OF NON-TROPICAL SPRUE

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In the course of treating a case of non-tropical sprue recently, the author had occasion to make an incidental observation on the behavior of the blood uric acid in this disease, which may be of considerable theoretical interest.

Case Report. The patient was a 19-year old Negro male, with a 3-month history of anorexia, weakness, weight loss, and vague abdominal pain. No other gastrointestinal symptoms were present, and particularly, bulky, foul-smelling stools were absent. Laboratory studies showed a marked macrocytic, "hyperchromic" anemia. The red blood cell count was 1.8 million per c. mm., and the mean corpuscular volume was 124 cubic microns. Bone marrow studies revealed a megaloblastic picture. The gastric contents contained no free hydrochloric acid, even after histamine stimulation. Roentgenographic study of the small bowel (Fig. 1) revealed segmentation and "puddling" in the ileum, often seen in sprue, though not diagnostic. The oral glucose tolerance and vitamin A tolerance curves were both flat. Analysis of stools revealed 38% total fat, with a normal proportion of fatty acids.

Blood chemistry studies were not remarkable, except for a blood uric acid level of 8 mg. per 100 cc. (normal in our laboratories is 2 to 5 mg. per 100 cc.). This was rechecked, and the second determination was 8.4 mg. per 100 cc.

Because of the absence of free hydrochloric acid in the gastric contents, and despite the patient's race, a diagnosis of pernicious anemia was made, and intramuscular therapy with vitamin B_{12} was begun, in doses of 15 mcg. daily. This was continued for 10 days, but there was no clinical or hematological response. It was, therefore, discontinued, and the patient was given refined liver extract intramuscularly, in doses of 15 units daily for 10 days. Again there was no clinical or hematological response, except for a rise in the reticulocyte count from an initial level of 1% to 2 or 3%. After the unsuccessful trials of B_{12} and liver extract, therapy was instituted with oral folic acid, 15 mg. daily. The patient had a prompt clinical response characterized by increased appetite and well-being within 24 hours, and within 48 hours the reticulocyte count began to rise, reaching a peak of 16% on the fifth day of therapy. Recovery was uneventful and complete, and the patient attained an erythrocyte count of 4 million within 6 weeks after therapy was started. Retrospectively, a diagnosis of non-tropical sprue was made. Fig. 2 presents a graphic summary of the hematological findings during the patient's hospital stay.

About 10 days after the institution of folic acid therapy, the blood uric acid analysis was repeated, and the value at this time was 6.4 mg. per 100 cc. Another recheck 3 days later showed a value of 6.0 mg. per 100 cc. This was considered somewhat surprising, since the variation in uric acid levels in this

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FIG. 1—Small-bowel study showing segmentation and "puddling" of the barium column in the ileum. This finding is often present in sprue, but is not diagnostic.

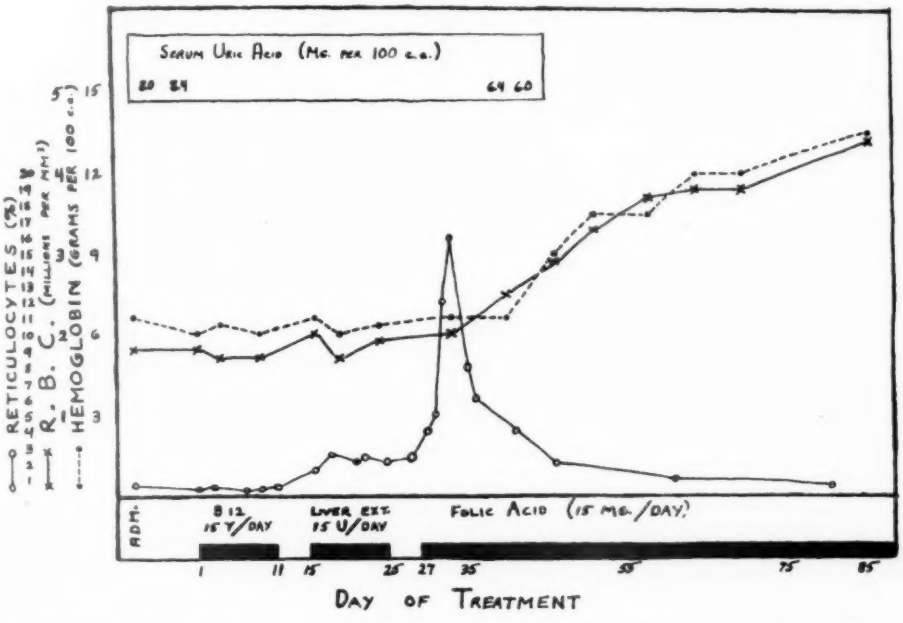

FIG. 2—Hematological findings during the hospital stay. Note the level of hemoglobin proportionately in excess of the erythrocyte level at the time of admission. The absence of any effect due to vitamin B_{12} is clearly visible. With the administration of liver extract, there is a slight rise in reticulocytes, but no change in RBC or hemoglobin. The course of events after folic acid therapy represents a classical picture for megaloblastic anemia: early reticulocyte crisis, followed by a gradual rise of RBC and hemoglobin. Note the relation of uric acid levels to the time of institution of folic acid therapy.

case was directly opposite to that usually seen in pernicious anemia. According to Wintrobe[5], the blood uric acid is generally normal in pernicious anemia in relapse, and rises promptly and significantly during remission.

Discussion. The following is offered as a tentative explanation for the findings in this case: It has been demonstrated[1] and repeatedly confirmed[2,4] that the level of xanthine oxidase in animal tissues is markedly elevated in the presence of folic acid deficiency, and drops to normal when this deficiency is remedied. Since xanthine oxidase catalyzes the oxidation of xanthine and hypoxanthine to uric acid, an increased activity of the enzyme could quite conceivably result in increased production of uric aid. If these results are applicable to humans, it may well be that the hyperuricemia in this case is an indirect result of folic acid deficiency. This is entirely consistent with the fall in uric acid level observed after folic acid therapy was begun.

A recent paper by Machlin *et al.*[3] lends experimental support to this hypothesis. These authors observed that in chicks on otherwise comparable diets, the blood uric acid level varied inversely with the folic acid intake, lower intakes being associated with higher blood uric acid levels.

Summary. A case of non-tropical sprue with megaloblastic anemia is described, in which it is noted that a high blood uric acid level was present during relapse. Following successful treatment of the anemia with folic acid, the blood uric acid level was observed to decrease markedly. Possible explanations for this are discussed, and theoretical and experimental evidence is cited to support the hypothesis that hyperuricemia may sometimes be a chemical sign of folic acid deficiency.

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AMINOACIDURIA IN CHILDHOOD: CYSTINURIA AND CYSTINOSIS*

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DURING the past 6 years knowledge of the amino acid composition of body fluids has increased considerably, due to the development of new assay procedures. Chemical methods had established the fact that normally 1 or 2% of the total urinary nitrogen was derived from amino acids but gave little or no information as to the relative amounts of the different amino acids excreted in the urine. Paper chromatography and the perhaps more quantitatively accurate, but also more laborious, microbiologic techniques have shown that there are normal patterns of amino acid excretion and deviations in certain disease states. This review will report some of the more important recent studies, using these two methods, which help define the nature and extent of amino acid excretion by normal individuals, and in two abnormal conditions, cystinuria and cystinosis.

Normal and Abnormal Amino Acid Excretion. Normally, the amino acids presented to the blood stream from digested dietary protein and liberated during the constant turnover of tissue protein are rapidly deaminated in the liver. The released carbon fragments are probably mainly converted into carbohydrate but may, with the exception of deaminated lysine and threonine[29], be re-aminated (transamination) to form new aggregates of amino acids and thus satisfy the needs of the body at that moment for pro-

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tein building blocks. Most of the nitrogen so released is converted by the liver into urea and excreted by the kidney. Urea nitrogen contributes, roughly, 80 to 85% of the total urinary nitrogen. From circulating serum glutamine and amino acids the renal tubule forms ammonia, the second major urinary nitrogen component. Finally, all but a small fraction of the large amount of amino acids filtered through the glomerulus is reabsorbed by the renal tubule, and that portion not absorbed, or possibly excreted into the tubule, appears in the urine as free amino acids and di- or tripeptides. It is not known why amino acids are excreted in the urine at all. It seems likely that their presence in the urine cannot be dismissed as simply a "leakage through the kidneys"[50].

In Table 1 are listed the amounts of the various amino acids excreted by normal children and adults. From inspection, several facts are evident. There is considerable variation from individual to individual in the amounts of the different amino acids excreted. This is particularly true of the "nonessential" amino acids, such as aspartic acid, glutamic acid, and serine. This appears to be true also of histidine excretion by the adult, and it is of interest that although considered one of the ten "essential" amino acids, histidine is not needed to maintain adults in nitrogen balance[51]. In contrast to this, the "essential" amino acids are generally excreted in very small amounts.

It is also apparent that the amounts excreted are loosely related to body size, the older child and adult excreting more than the infant. This is not due to differences in the amount of dietary protein alone: there is no direct correlation between protein intake and amino acid output[57,60,64], as there is between protein consumption and urea excretion. However, the feeding of unbalanced or inadequate diets[57,70], or the ingestion or infusion

TABLE 1.—URINARY AMINO ACID EXCRETION
mg./24 hr.†

Amino Acid	*Infants and Young Children*	*Older Children and Adults*
Alanine	0–13[a] (—36)[b]	18–121[b,e]
*Arginine	0–7[f]	12–45[d]
Aspartic Acid	0–29[a]	87–259[d]
Cysteine-cystine	0–22[a,c]	45–138[d]
Glutamic Acid	0–34[a]	102–770[d]
Glycine	0–44[a,c]	79–165[c]
*Histidine	8–30[c]	65–560[d,e]
*Isoleucine	0–3.5[c]	12–33[d]
*Leucine	0–8[a]	12–40[d]
*Lysine	1.5–12[c]	36–166[d]
*Methionine	0–1.5[c,f]	4–15[d]
*Phenylalanine	1–4[c]	10–45[d]
Proline	0–12[a]	23–62[d]
Serine	0–17[a]	25–304[e]
*Threonine	2–13[f]	25–175[e]
*Tryptophane	0–7[c,f]	11–86[d]
Tyrosine	0–7.5[a]	23–100[d]
*Valine	0–7[a]	7–60[e]

Determined by paper chromatography: a—Souchon.[59] Determined by microbiologic assay: b—Schreier,[55] c—Schreier,[56a] d—Woodson,[71] e—Steele,[60] f—Eberlein.[27]

† Values are for unhydrolyzed urine.

* Ten "essential" amino acids.

of artificial amino acid mixtures[28,42,56a], at least temporarily leads to increased amino acid excretion. Possibly subtle dietary variations explain in part the differences in amino acid excretion among normal individuals. In the case of the infant, the amounts excreted are directly related to the urine volume[56a]. All things considered, it is remarkable how constant the urinary excretion pattern normally remains from day to day[5,63].

An abnormal excretion of amino acids has been found primarily in diseases affecting the two organs most concerned with amino acid metabolism, the liver and the kidney. Perhaps the best known example is "acute yellow atrophy" of the liver, in which such large amounts of certain amino acids are excreted that they precipitate in the urine. The blood levels of some amino acids may be greatly elevated during the acute stage of severe hepatitis[54,56b], due to faulty deamination and impaired hepatic storage. The renal tubule appears unable to reabsorb the resultant large amounts of amino acids filtered through the glomerulus. Under less trying circumstances the liver deaminates amino acids adequately, so that while there may be[58], there is usually not[22,26] excessive aminoaciduria during the course of liver cirrhosis. The blockage of conversion of phenylalanine to tyrosine, found in phenylpyruvic oligophrenia[39], may be due to a specific, liver enzymatic disturbance. Because of this block, phenylalanine accumulates in all the body fluids and the renal tubular reabsorption capacity is exceeded. In addition, it may be that a temporary liver impairment, associated with excessive tissue breakdown, or diminished protein synthesis, explains the transient aminoaciduria seen in experimental animals and in patients treated with ACTH or cortisone[11,38]. Both of these compounds may also act directly upon the renal tubule.

In all these conditions the aminoaciduria is associated with an aminoacidemia of variable degree. This is not the case, however, in another form of liver disease, hepato-lenticular degeneration, in which the excessive amino acid loss seems to be due to renal tubular dysfunction[15]. The marked aminoaciduria found in nephrosis[55] undoubtedly reflects the underlying and otherwise evident tubular damage. It is probable that there is some type of tubular dysfunction causing the excessive loss of amino acids found in cystinuria and in cystinosis, as well.

Cystinuria. The frequency of cystinuria in children is not known. The serious complication, the formation of cystine stones in the urinary tract, is certainly not commonly encountered in pediatric practice. And yet it was from the urinary stone of such a child that Wollaston, in 1810, first isolated cystine, many years before the amino acid was detected in protein. Since, for unknown reasons, most individuals with cystinuria never form stones, the incidence of the disorder can only be measured by laboratory methods. Using the sodium cyanide-nitroprusside test for cystine, Lewis[43], in 1933, found positive reactions, on repeated tests, in the urine of 40 men and women among 10,534 students he examined, an incidence of about 1:265 in a healthy college population. Only 4 of these students showed cystine crystals in the urine. The incidence of this hereditary disorder, probably transmitted by a recessive gene[12,23], might well be equally high in childhood.

It has often been demonstrated that the usual urinary sulfur partition is disturbed in such individuals. The normal adult excretes approximately

1 gm. of sulfur daily, partitioned as follows[3]:

Inorganic sulfate	90%
Ethereal "	5%
Unoxidized " (cystine)	5%

The patient with cystinuria may excrete the same total amount of sulfur, but largely as free cystine:

Inorganic sulfate	40%
Ethereal "	5%
Unoxidized "	55%

Experiments have shown that the feeding of cystine to such individuals leads only to an increased excretion of inorganic sulfate, whereas feeding cysteine or methionine, its precursor, leads to an increased excretion of cystine[14]. It was presumed that in this condition the kidney did not "handle" cysteine normally[10]. This, of course, does not adequately explain the disturbance. Dent[24] has pointed out that there is no elevation of the blood cystine level in such individuals and, even more important, that not only cystine is excreted in excess, but also lysine, arginine, and the products derived from them by bacterial decomposition, cadaverine and putrescine. Yeh and collaborators[72] had reported the same findings previously. Accordingly, Dent reasons, the abnormality is probably not a vague cystine-cysteine metabolic disturbance but a defect of renal tubular reabsorption, affecting amino acids with a closely related structure (diamino acids). (Fig. 1.)

Since, of the three, cystine is the least soluble in an acid medium, it easily precipitates in the urinary tract. This theory would seem to explain the increased cystine excretion by such individuals following the ingestion of cysteine and methionine, for both amino acids are readily converted into cystine. Cystine itself, given orally, does not increase this loss because it is poorly absorbed from the intestine and is probably completely oxidized by the intestinal bacteria.

While individuals with cystinuria may excrete up to 1 gm. of cystine daily, in contrast to the normal adult loss of less than 150 mg., they usually grow and develop normally. There is the constant risk of cystine stone formation, however, and such stones may cause renal colic, urinary tract obstruction, and hydronephrosis. The stage is then set for secondary bacterial infection, which may progress to chronic pyelonephritis, renal insufficiency, and death in uremia. Because the stones are pure cystine they are not usually visualized by Roentgen-ray. In the absence of stone formation, cystine crystals are usually not found in the urine sediment. It is obvious that chemical and chromatographic methods greatly assist in making the diagnosis. The only treatment of value in these cases, aside from surgery and chemotherapy as indicated, is an alka-

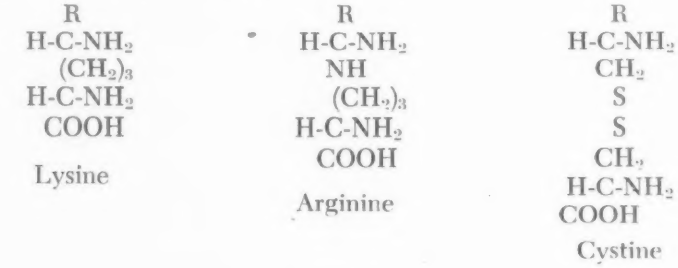

Fig. 1

line ash diet and alkaline salts to prevent the constantly excreted cystine from precipitating in the urinary tract.

Cystinosis (deToni-Fanconi Syndrome). Compared to cystinuria, the de Toni-Fanconi syndrome, or cystinosis, has been known for only a short time, but its history is much more complicated. In 1903, Abderhalden[1] reported chemical examinations carried out on tissue from a 21-month-old Swiss infant dying of "inanition". Macroscopically the liver and spleen were covered with white flecks, which under the microscope proved to be accumulations of hexagonal and round crystals. Abderhalden showed that these were cystine crystals. He tested the urines of the entire family for cystine, since two other siblings had previously died with identical complaints, and was able to isolate relatively large amounts from the urine of the two living siblings, less from the urine of the father and paternal grandfather. This led him to label the disorder a "familial cystine diathesis". He attributed it to a specific abnormality of protein breakdown. In 1924, the Dutch pediatrician Lignac[44a] reported 3 similar cases in children between the ages of 14 months and 3 years. All three had shown stunted growth, severe rickets, "severe renal disease", and progressive inanition. At necropsy, there were widespread cystine deposits, in one child cystine stones in the renal pelvis and ureter, and in all three moderate cloudy swelling of the tubular epithelium or mild interstitial nephritis. Subsequently, two cases were reported from England[53]. One child had early evident rickets, a low-normal serum phosphorus at age 11 years, but never cystine crystalluria. Both he and the second child probably died in uremia and had extensive renal glomerular and tubular damage at necropsy, in addition to cystinosis. A more detailed case report by Beumer[6] in Germany added to the above findings albuminuria, glycosuria, and only terminally an elevated serum non-protein nitrogen level. All these authors considered the disease a severe form of the otherwise benign cystinuria[44b].

Meanwhile, in 1931, Fanconi[31a] briefly described finding rickets and stunted growth in a child with albuminuria and glycosuria. Two years later, de Toni[65] reported a dwarfed child with vitamin D-resistant rickets and spontaneous fractures, who showed a low serum phosphorus, acidosis, pronounced glycosuria, and albuminuria. With a similar case reported by Debre, the one of de Toni, and two more of his own, Fanconi[31b,c], in 1936, established a syndrome, "nephrotic-glycosuric dwarfism with hypophosphatemic rickets". Comparing this report with their findings in a case of cystinosis, Beumer and Wepler[8] shortly thereafter came to the conclusion that cystinosis and the Fanconi syndrome were identical. This was proved when at necropsy one of Fanconi's original cases showed "cystine storage disease"[46]. Since then there have been a fairly large number of similar cases reported from Holland[4,18,20], Switzerland [37,49], England[9,22,61,69], Germany[45,66,68], and Scandinavia[25]. Guild[36] reported the first case in this country in 1937. There have been several such cases subsequently described in the American literature[21,34,35,40,47,48].

The syndrome has been seen in adults[22,61] much less frequently than in children, in males apparently as frequently as in females. There is often a history of consanguinity[31c,47,68]. Frequently, siblings have died from the same disorder[1,21,45,53], and in at least one instance[17] identical twins have been affected. It is presumed that the

disease is transmitted as a recessive[31c], although it may be a dominant[66], gene.

Typically, an infant with cystinosis grows and develops normally during the first 6 to 8 months of life. The parents then note refusal of feedings other than liquids, the development of polyuria, and cessation of growth. The infant may be brought to the hospital in a "crisis", with fever, dehydration, and acidosis. In older children the bone deformities due to rickets and photophobia are often striking. An occasional patient may be referred to the hospital for suspected diabetes. Physical examination may disclose florid rickets which has developed in spite of adequate vitamin D prophylaxis, marked dwarfing (a height age of 6 at chronologic age 11 years, for example[66]), severe malnutrition, variable fever associated with dehydration, and occasionally enlargement of the liver. The skeletal musculature may be very flabby and hypotonic[9]. The blood pressure is usually normal initially but often rises as the renal disease progresses. Occasionally there may be no bone disease seen by Roentgen-ray[9], or the bones may even appear excessively dense[37], the cranial vault overgrown[33]; but almost all patients show rachitic changes, or at times spontaneous fractures[47,65] or pseudofractures[61] in the older age group.

Marked abnormalities are found on examination of the urine and the blood. Polyuria is frequent and may be extreme, suggesting diabetes insipidus, particularly when the urine specific gravity is fixed. The urine may be acid or alkaline, often with a distinct ammoniacal odor. Albuminuria with the presence of occasional white blood cells is common. Glycosuria is variable: it may not be apparent on first examination, or it may be intense, for such patients have excreted up to 20 gm. of glucose daily[47]. Paper chromatography may show the presence of an abnormal amount of glucose in the urine when Benedict's reagent does not[9]. There is some evidence that the glycosuria increases as the disease progresses. There is usually marked phosphaturia and variable hypercalcuria[34,35,48], the latter probably depending upon the amount of vitamin D previously administered. Kidney function tests may not be remarkable early in the disease but usually show impaired concentration of the urine and diminished phenolsulfonphthalein excretion later on. Associated with these urinary findings are acidosis and at times organic acidemia[61]. The serum phosphorus level is most commonly very low but may be elevated at a seemingly early stage of the disease[9]. While it may subsequently fall[20], it usually rises along with the non-protein nitrogen level as renal function becomes more impaired. The serum calcium level is usually fairly normal but may be so low that tetany results[53]. When there is active rickets the serum phosphatase level is elevated, but it may be normal otherwise. During a crisis, there is often a low serum potassium level[25] with associated electrocardiographic changes[9]. The serum proteins are normal[45] or there may be a moderately lowered albumin and elevated alpha and beta globulin fractions[68]. The fasting blood sugar level may be low, normal, or somewhat high. Equally variable are the results of the glucose tolerance test, which may be a hazardous procedure in those patients with hypokalemia: symptoms of shock may appear and death apparently has resulted in at least one instance[31b]. Liver function tests show little abnormality[33,68].

In his original description of the syndrome, Fanconi[31c] postulated that

the increased organic aciduria found in such patients was due to amino acids. McCune, Mason and Clarke[48] were the first to show that at least 80% of these organic acids excreted were in fact amino acids. Paper chromatographic studies have further shown that usually 10 or more amino acids are excreted in excessive amounts and that the pattern is rather constant in a given case, the loss increasing as the disease progresses. This is in marked contrast to cystinuria; and indeed in cystinosis, cystine is usually not excreted in excessive amount. The conflicting reports of elevated serum amino acid levels in one case[9,68] and normal levels in another[22] show that either may be found. However, in most of the reported cases the total amino acid nitrogen level of the blood has been normal.

The pathologic changes seen at necropsy in this disease have depended somewhat on its duration, and consequently the cause of death (probably from hypokalemia during a "crisis" and from uremia in late stages), as well as on the care exercised to avoid dissolving out cystine crystals in the tissue sections. This readily happens when formalin or other aqueous preservatives and fixing solutions are used, instead of 95% alcohol. It may be that not all cases of the de Toni-Fanconi syndrome will show cystine deposits at necropsy[31d,32]; however, the fact that Bickel[9] was able to demonstrate them in all 17 of his patients antemortem suggests that crystals will be found, if only microscopically, when proper search is made for them.

The bone changes at necropsy are those of rickets or osteomalacia. When there has been considerable renal damage there is superimposed bone reabsorption. Albright's osteitis fibrosa generalisata[2], resulting from secondary hyperparathyroidism. The kidney changes vary from slight cloudy swelling of the tubular epithelium[61] to tubular necrosis[40], and even to extensive glomerular damage, with arteriolar lesions of the type found in malignant hypertension or chronic glomerulonephritis[52,53]. There are occasionally congenital anomalies of the urinary tract[40]. Cystine crystals, when found, may be insterstitial but usually are accumulated in large phagocytic, reticuloendothelial cells, primarily in the liver, spleen, lymph nodes and bone marrow. The wide distribution of the crystals makes possible the diagnosis of cystinosis during life. Cystine may be found by lymph node or bone marrow biopsy[30], by biopsy of the conjunctiva[13a,b], which may be preferable, or by slit lamp examination of the cornea[68]. The crystals may be positively identified as cystine by Wollaston's test (needles form when hydrochloric acid is added), polarized light, various chemical tests (sodium cyanide-nitroprusside, beta-naphthaquinone-sodium sulfate), or paper chromatography. Paper chromatographic examination of the urine is undoubtedly the best method for detecting such cases in an early stage, although more than one examination may be necessary[9].

The cause of the de Toni-Fanconi syndrome is unknown. Comparing its clinical picture with that of cystinuria, one is at first sight at a loss to understand why both are considered variants of the same underlying hereditary disturbance by most European authors[33] (Table 2). There are, however, several case reports which suggest this relationship. Abderhalden's[1] finding of excessive cystine in the urine of the siblings, father and grandfather of a patient is most frequently cited. Paternal cystinuria occurred in a case reported by van Creveld[19], cystinuria in a sibling of Hottinger's case[37], and finally cystine stones in the ureter and

renal pelvis of a patient with cystinosis described by Lignac[44a]. It is known that a patient with cystinosis may excrete a large quantity of cystine in the urine, although this is not the rule, as it is in true cystinuria. The "cystinuria" of the de Toni-Fanconi syndrome is only part of the picture even when it does occur, and excessive amounts of 10 or more other amino acids are excreted in the urine at the same time. One cannot be certain that the cystinuria reported in the siblings of patients with cystinosis was benign cystinuria, for these urines were examined only by chemical tests and not by chromatography to reveal the presence of other amino acids. The amounts excreted by the father and grandfather of Abderhalden's case, 9.2 and 14.0 mg. per 100 cc., may not have been really excessive. Finally, Dent's discovery of the Fanconi syndrome in adults also suggests that possibly the adults investigated by Abderhalden and van Creveld did not have benign cystinuria but a mild type of the Fanconi syndrome. More intensive studies of this problem are needed.

Neither the underlying metabolic defect nor the resultant sequence of changes in cystinosis is clearly understood. Initially, the albuminuria, glycosuria and rickets were stressed, and Fanconi[31b,c] felt that there was an underlying renal tubular defect of reabsorption. The subsequent demonstration of cystine deposits in most such patients led him and others to suspect a generalized disturbance of protein metabolism, possibly disturbed deamination[31d,32], the renal damage arising secondarily. This has not been supported by the finding of normal serum amino acid levels in most patients, and even in those with somewhat elevated levels, cystine is found in normal amounts in the blood. Dent[22] could not demonstrate a disturbance of the metabolism of methionine, a precursor of cystine, in his adult cases. Nor does the normal serum protein fractionation by electrophoresis support this theory, and the usual liver function tests are also normal. The cause of the deposition of cystine in such patients is completely unknown. It does seem well established that cystine fed to young, but not older, experimental animals will produce renal damage similar to that seen in Fanconi's syndrome[7,44a], but cystine storage does not occur. It

TABLE 2.—COMPARISON OF CYSTINURIA AND CYSTINOSIS

	Cystinuria	*Cystinosis*
1. Age at which symptoms appear	Adulthood (uncommon in childhood)	Infancy and childhood
2. Growth and development	Normal	Markedly retarded
3. Rickets and osteomalacia	None	Almost invariable
4. Serum phosphorus level	Normal (rises with renal damage)	Usually low, rises with renal damage
5. Glycosuria	None	Common
6. Amino acids excreted in excessive amounts	Cystine, lysine, arginine	10 or more, usually not including cystine
7. Cystine stone formation	Common	Very rare
8. "Cystine storage"	None	Almost invariable in cases in childhood, not found in adult cases

is not known why cystine deposits have not been found in human adults with other manifestations of this syndrome.

Of great interest is Stowers and Dent's[61] report of an adult case falling into the category of the de Toni-Fanconi syndrome, in which there was complete absence of phosphatase, by Gomori's stain, in the proximal convoluted tubule, the presumed site of glucose, phosphorus and amino acid reabsorption. The suggestion had been made in one of Fanconi's[31c] early papers that a disturbance of renal phosphatase could explain the urinary findings and the rickets. Recently, Fanconi[32] reported a case of glycogen storage disease of the liver with acidosis, hyperphosphaturia, and aminoaciduria, and most recently Cori[16] has shown an absence of hepatic (glucose-6-) phosphatase in several cases of von Gierke's disease[16]. Taken together, these three reports strongly suggest a related enzymatic disturbance in cystinosis. Studies of phosphatase activity in liver and kidney tissue would seem to be indicated in this disease, which is by name at least also a "storage" disease.

Until recently, it could be said that all cases with this syndrome died in infancy or childhood. It is now known that some such patients reach adulthood, only then to die of severe liver disease[22]. However, the recent preliminary report by Bickel and Smellie[9] perhaps permits this review to end on a somewhat more optimistic note. These authors describe rather dramatic healing of the rickets (which has only temporarily improved in the experience of others), and even more surprising, a diminution or disappearance of the aminoaciduria in children with proved cystinosis, whom they treated with Shohl's citric acid-sodium citrate solution, added potassium chloride, and moderately high doses of vitamin D. Should this prove to be the experience of others, the technique of paper chromatography, which detected most of these authors' cases, will indeed have demonstrated its value in clinical medicine.

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THE HEART IN PREGNANCY

Review of Recent Studies of Cardiovascular Physiology and Heart Disease

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DURING the past decade maternal deaths due to cardiac disorders have not declined in number as rapidly as have those associated with the common obstetrical complications of pregnancy. Indeed, in certain large obstetrical clinics, heart disease is now replacing such complications as a major cause of maternal death[98,136]. Moreover, it is probable that in forthcoming years increasing numbers of adolescent girls handicapped by cardiac defects will survive to child-bearing age as a result of current efforts to alleviate such defects surgically. It would appear appropriate, therefore, to review the significant contributions to the subjects of maternal cardiovascular physiology and heart disease that have appeared since the publication, in 1941, of Hamilton and Thomson's well-known monograph in this field[51].

Cardiovascular Changes During Pregnancy. CARDIAC POSITION AND CONFIGURATION. Roentgenographic studies demonstrate that the heart is displaced upward, laterally, and forward as pregnancy advances[78]. Its transverse diameter may be increased by as much as 1 cm.[51,80]. The ratio of the cardiac width to that of the thorax may exceed 50%. The apex impulse is frequently diffuse, and may be displaced upward to the fourth left interspace, and outward to or beyond the mid-clavicular line[34].

By fluoroscopy, the anterior wall of the barium-filled esophagus may be seen to be indented by the left auricle when viewed in the right oblique position[61]. This may erroneously suggest mitral valvular disease, particularly since the left border of the heart occasionally appears straightened in the antero-posterior view[61]. Schwedel believes that the above changes of configuration are due principally to elevation of the diaphragm and to lordo-

sis[124]. He suggests that deep inspiration and slight forward bending be employed during fluoroscopy to counteract the effects of lordosis and diaphragmatic elevation.

There may also be some actual hypertrophy or dilatation of the heart. Such a possibility is supported by the observation that changes in cardiac outline may occur at an earlier stage in pregnancy than would be anticipated from the effect of diaphragmatic elevation alone[34].

CARDIAC AUSCULTATORY CHANGES. Extrasystoles are increased in frequency during pregnancy, occurring in about 15% of women[34]. They are often associated with palpitation[70]. Triple rhythm is not uncommon[10]. The first sound is loud at the apex, and the second sound is accentuated in the pulmonic area[34]. Cohen and Thomson state that a soft, short, apical, systolic murmur is heard in about 50% of normal pregnant women, and a similar murmur is almost always heard in the second left interspace near the sternum[23].

PULMONARY CHANGES. The elevated diaphragm encroaches upon the lungs, especially at the right base, where fine rales may be heard[71]. These disappear after coughing or deep breathing. During pregnancy, therefore, basal rales should be attributed to pulmonary congestion only when they are persistent[71]. The pulmonary vascular markings and conus may be prominent[61].

BLOOD. Beginning about the ninth week of pregnancy, the blood volume increases progressively, usually reaching a maximum about the 7th or 8th month. It then decreases slowly toward term, but still remains above its prepregnancy level. The data of recent investigations indicate that the maximal total increase of blood volume during pregnancy averages about 30% of prepregnancy values, the plasma volume 40%, and the red cell volume 20%[19,29,30,31,90,112,113,139,142]. Because of the greater increase in plasma volume, there is a reduction in hematocrit and in blood viscosity[32,107]. The red cell count is diminished by about 750,000 cells per c.mm., and the hemoglobin by approximately 2.0 gm. per 100 cc.[34]. Plasma protein concentration may fall to as low as 5.5 gm. per 100 cc.[34].

Several explanations have been advanced to account for the changes that occur in the maternal blood during pregnancy. Burwell's well-known concept holds that the placental site acts as an arteriovenous fistula, and that the changes in maternal blood are similar to those identified with such fistulas[16]. However, this attractive hypothesis does not account for increases in blood volume that may occur as early as the 9th week of gestation (that is, before the placental circulation is well established), nor does it explain the decrease in volume noted after the 8th month[51,71]. Changes in sodium and water metabolism are also undoubtedly implicated. Chesley has demonstrated that water retention is a normal feature of pregnancy[21]. He has found, however, that this fluid retention ceases during the last weeks of gestation, and that many patients then begin to lose water[20,22]. Loss of water continues during the puerperium. Crabtree, and others also, have observed such fluid loss[27,138]. Taylor *et al.*, on the other hand, have found that sodium retention continues until delivery, and that its loss first occurs in the post-partal period[138].

To explain the cardiovascular changes which occur late in pregnancy, McGaughey suggests that an increased resistance develops in the so-called placental shunt[87]. It is his contention that increasing volume and tortuosity of the chorionic villi of the placenta increase the resistance to the flow of maternal blood in the intervillous spaces[28,32,79]. He also suggests that the

stretching of the uterine muscle in late pregnancy (as opposed to the hyperplasia and hypertrophy which occur earlier) compresses the maternal vessels and thus increases vascular resistance[42]. He cites evidence adduced by several investigators to indicate that an increase in peripheral vascular resistance can bring about changes of the type often seen in late pregnancy, namely, an increase in systolic and diastolic blood pressures, narrowing of pulse pressure, and hemoconcentration[7,55]. Germane to these considerations is the well-known fact that surgical occlusion of an arteriovenous shunt can be followed by hemoconcentration and by increases in arterial blood pressures[63,74].

Barcroft has shown that in the pregnant rabbit the oxygen saturation of the uterine venous blood drops rather suddenly toward the end of gestation[3,4]. This finding lends some support to McGaughey's belief that in human pregnancy there is a decrease in the effectiveness of the placental vascular shunt as term is approached. Palmer and Walker have supplied additional evidence[100]. They performed cardiac catheterizations upon women during late pregnancy and found that blood containing less oxygen than the maternal "mixed venous" blood is added to the circulation during a uterine contraction. (However, see comment on Palmer and Walker's technique under discussion of cardiac output.)

CARDIAC OUTPUT. With one exception[149], all investigators report an increase in cardiac output during pregnancy. The observed alterations of cardiac output roughly parallel the changes in blood volume. An increase in output has been demonstrated by the acetylene, ethyl iodide, nitrous oxide and cardiac catheterization techniques[17,40,52,56,82,83,100,123,132,133,148]. Observations differ as to the time of onset of the increase, and also as to the time in pregnancy at which it reaches its maximum. Schmidt[123], Gammeltoft[40], and Palmer and Walker[100] found that the rise begins as early as the 9th week of gestation. Burwell[17] found that it begins at the 13th week, Hamilton[52] between the 10th and 13th weeks, while Stander and Cadden[132] state that it begins at the 4th month.

Most observers find that cardiac output attains its maximal increase during pregnancy between the 26th and 32nd weeks. After this, it falls gradually, although at term it is still higher than it is in the non-pregnant state. The maximal increase is equal to 25 to 50% of the normal non-pregnancy values. Palmer and Walker, however, using cardiac catheterization, found that the output rose abruptly at the 9th week, remained high to the eighth month, then fell somewhat[100]. They collected blood samples from the right auricle. (Burwell, studying 4 patients by the acetylene technique, found that it did not begin to fall until after the 9th lunar month[17].) Warren *et al.*, have pointed out that the right auricle receives blood of widely varying oxygen content; hence, blood samples obtained from the auricle may vary considerably in oxygen content and may not be representative of mixed venous blood[145]. Hamilton, also employing cardiac catheterization, found the output rises gradually starting about the 10th to the 13th week, reaching a maximum around the 29th week[52]. He, too, used right auricular blood, but placed his catheter by a different technique than that employed by Palmer and Walker. The technique used by Hamilton had been previously studied by Cournand *et al.*, and had been shown to yield right auricular blood samples of excellent constancy with respect to oxygen content[26].

Werko is the only observer who has not found an increase of cardiac output during pregnancy[149]. He used a

cardiac catheterization technique, but obtained his blood samples from the pulmonary artery. In his study, increased oxygen consumption was offset by an increase in arterio-venous oxygen difference.

OXYGEN CONSUMPTION. The basal metabolic rate during pregnancy remains unchanged until the 2nd month, but rises progressively thereafter, attaining a peak at term[65,108,120,121,130,147]. The maximal increase is small, however, ranging between +5 and +25%. Sandiford and Wheeler believe that this elevation can be accounted for by the metabolism of the fetus and placenta alone[120]. While this explanation has been challenged, and hyperplasia of the thyroid gland has been suggested as the cause of the increase, little evidence for such hyperplasia can be found[54,65,68,115]. Peters finds that although the maternal precipitable serum iodine rises appreciably shortly after the beginning of pregnancy, the level remains constant thereafter and does not parallel the rise in the basal metabolic rate[103,104]. This suggests that there is no progressive increase in maternal tissue metabolism.

VENOUS PRESSURES. Pressures in the *antecubital veins* remain practically unchanged during pregnancy[51,89]. According to Werko, pressures in the *right auricle, right ventricle* and *pulmonary artery* are lower, by several millimeters of mercury, than in non-pregnant women[149]. Other observers, however, find right auricular pressures normal or slightly elevated[52,100]. Pressures in the *femoral veins* rise steadily during pregnancy, reaching a maximum of 24 cm. of water at term[15,89]. That this rise is due principally to the impingement of the gravid uterus upon the pelvic veins, and the consequent retarding of blood return from the legs, has been demonstrated by radioactive sodium clearances[154,155]. This retarded blood flow is doubtless a factor in the occurrence of ankle edema which many healthy pregnant women observe at the end of a day's activities. The same pressure changes are undoubtedly partly responsible for the aggravation of varicosities of the sapheno-femoral and vulvar veins observed between mid-pregnancy and term.

CARDIAC WORK AND ARTERIAL BLOOD PRESSURE. In obstetric literature the terms "cardiac output" and "cardiac work" are used loosely and interchangeably. In the physiologic literature, however, the meaning of the former term is limited to defining the volume of blood ejected by the heart in a given unit of time, whereas cardiac work is considered to represent the combined effects of (a) the cardiac output, (b) the pressure head (blood pressure) against which this output must be ejected, and (c) the work done in imparting velocity to the aortic stream[35,111,134]. Cardiac work can be estimated by the use of the formula: Cardiac output X mean arterial blood pressure $+\frac{MV^2}{2g}$.* For many purposes, approximations of cardiac work can be made by omitting the factor for kinetic work (about 2% of the total work, unless stroke volume is abnormally large and diastolic pressure abnormally low, according to Remington, *et al.*[111]) and using: Work = cardiac output X mean arterial blood pressure[35,111,134]. Weiss, in 1924, attempted to calculate cardiac work during pregnancy, and estimated that it was increased about 45% above normal[148]. However, his

* M=mass of blood ejected; V=mean ejection velocity in cm./sec. computed from: $V=\frac{\text{cardiac output per second}}{\text{cross sectional area of aortic root}}$; g=acceleration due to gravity. This formula differs from the ideal by the substitution of mean values for integrals, and refers only to the work of the left ventricle, since the pulmonary arterial pressure is not considered[35,111,134].

pioneering efforts were limited to a small number of observations made during late pregnancy, and they included no control data. Although it is known that both the systolic and diastolic blood pressures are often low from the 4th through the 9th lunar months of gestation, this depression is hardly capable of neutralizing the increased cardiac load represented by the augmented cardiac output. Collateral evidence in support of this assumption is the observation that 20% of women affected with heart disease develop congestive failure for the first time during a pregnancy.

CARDIOVASCULAR PHENOMENA DURING AND FOLLOWING LABOR. In contrast to the wealth of data available concerning cardiovascular dynamics during pregnancy, little precise information has been assembled with respect to the effects of labor and delivery upon the maternal circulation. Attempts have been made by Stahler and Sampson to measure total maternal oxygen consumption during parturition[119,131] Their estimates suggest that the energy expended may be equivalent to that used in heavy work. An important component of the total effort is doubtless contributed by the parturient's straining activities in the second stage of labor. But Woodbury's studies of uterine contractions indicate that the energy expended solely in the involuntary activity of that organ must be considerable[153]. The other effects of labor and delivery upon the maternal circulation are known only in terms of bed-side observations of the maternal pulse, and of arterial and venous pressures.

The phenomena attending the gradual reversal of the profound cardiovascular changes of pregnancy during the early post-partal weeks have been more fully studied. New contributions to our knowledge of them have been referred to briefly in a preceding section. One aspect of these involutional changes has recently commanded special interest. Careful study indicates that during the hour immediately following delivery there is a sudden diminution of the maternal blood volume, amounting in some instances to as much as 900 cc. in excess of apparent external blood losses[84b]. This contraction of volume is a temporary one, however, inasmuch as serial measurements reapproach pre-delivery values during the ensuing 24 hours. At that time the well known phenomenon of post-partal diuresis begins to exert its effects upon blood volume, and the latter then begins its second, and final gradual return to pre-pregnancy levels. If the findings of these studies are correct, they may indicate the existence of "functional pools" available to the maternal organism for absorbing the mass of blood presumably thrown into the general circulation when the emptying of the uterus suddenly closes the capacious vascular bed of that organ. Thus, one of the mechanisms by which a climactic cardiovascular load is compensated for may have been more clearly revealed than has hitherto been the case.

Organic Heart Disease in Gravid Women. FREQUENCY. Organic heart disease was stated by Hamilton in 1941 to have been encountered in 1.7% of 48,000 pregnant women seen at the Boston Lying-In Hospital[51]. Estimates of its current prevalence in various obstetric centers reveal no significant change in this figure[50,93,136]. Approximately 90% of such disease is of the inactive rheumatic variety. Three to six per cent is congenital in origin. Arteriosclerosis, hypertension, syphilis, and hyperthyroidism account for most of the remaining cases.

DIAGNOSIS. When considering the diagnosis of organic cardiac disease during pregnancy, the physiologic changes previously mentioned must be kept in

mind. The presence of functional murmurs, physiologic alterations of cardiac contour, or symptoms suggestive of an effort syndrome may lead the inexperienced examiner to make a diagnosis of organic heart disease when no such disease is present. It is, therefore, especially important during pregnancy to employ fluoroscopy and roentgenography if there is doubt concerning the existence of cardiac enlargement or pulmonary congestion[71,124]. The recent diagnostic techniques of angiocardiography, roentgenkymography, and cardiac catheterization may also be helpful during pregnancy[25,96].

PROGNOSIS DURING PREGNANCY. 1. *Maternal Mortality.* Recent estimates indicate that the overall risk of maternal death in heart disease probably should not exceed 5%, although a rate as high as 50% has been reported[71,101,127]. The principal proximate cause of death is, of course, congestive cardiac failure. This complication accounts for approximately half of the recently studied deaths[60,143,71]. Complications such as acute rheumatic carditis, subacute bacterial endocarditis, embolic and obstetric accidents, taken together, account for most of the remaining half. The two periods of greatest danger with respect to the development of failure fall, as Hamilton has emphasized, during the 7th and 8th months of pregnancy, and during the interval encompassing the later stages of labor and the first post-partal days[60,143]. Recent estimates indicate that the threat of failure is about the same in both periods. The successful avoidance of this accident during the pre-partal period gives no assurance that it may not supervene during or after delivery. On the other hand, it is probable that most intra- and post-partal failures occur among women who have survived similar pre-partal episodes or imminent threats thereof[71].

2. *Functional Factors Influencing Prognosis.* The past decade has confirmed that, in the examination of any woman having a heart lesion who contemplates becoming pregnant, the best estimate of her fitness for this undertaking is to be had by considering the functional capacity of the heart rather than the anatomic aspects of her lesion[57,102]. For the majority of patients, there is a clear correlation, other things being equal, between maternal risk and the degree of functional impairment of the heart as defined by the American Heart Association's classification. Thus, studies indicate that under good management the risk of a mortality for patients in Classes I and II will probably average less than 5%, whereas for those in Classes III and IV it will be in excess of 10%[71]. In patients with definite cardiac enlargement, between 5 and 10% will probably fail to survive the pregnancy. Particular features which usually have ominous significance in prognosis include: Manifest or suggestive episodes of congestive failure; repeated hemoptysis associated with mitral stenosis; fibrillation; and severe arterial hypertensive disease[12,114,151,81].

3. *Pathologic Factors Influencing Prognosis.* In the pregnant woman having chronic rheumatic heart lesions, the recrudescence of acute rheumatic carditis is a grave complication[18,75,88]. Death is most likely to occur between the 24th and 36th weeks or within the immediate post-partal period. Fortunately, this complication is rare.

Developments resulting from the study and surgical treatment of congenital cardiac defects in children have stimulated increased interest in these lesions as they are encountered in pregnant women. The most frequently studied lesion has been patent ductus arteriosus; the maternal mortality of unoperated patients has been re-

ported as low as zero and as high as 20%[51,85,92]. For patients with septal defects, or pulmonic stenosis, or both, functional capacity, as in rheumatic heart disease, is the major consideration. Two instances of ventricular septal defects affecting both mother and child have recently been reported, the obstetric outcome having been favorable in both cases[85,140]. Where trouble has been met with in congenital lesions, it has generally followed the pattern observed in rheumatic lesions, namely, congestive failure during the late months of gestation or following delivery[57]. The characteristic complication of subacute bacterial endocarditis is also to be feared. However, there is no convincing, newly recorded evidence that pregnancy pre-disposes the patient to this complication, nor is the treatment of it as difficult and unrewarding as was formerly the case[72].

Although coarctation of the aorta is not a cardiac defect, mention of it in this discussion appears justifiable. Studies of more than 60 such lesions in pregnant women have recently been reported[1,6,48,77,91,92,94, 96,97,106,135,141,143, 144]. The composite maternal mortality rate has been 11%. Death is characteristically the result of a vascular accident. Alarming elevations of blood pressure are common during pregnancy, and particularly during labor[6,48,77].

4. *Therapeutic Factors Influencing Prognosis.* Modern studies of cardiovascular physiology, by clarifying the principles of treating cardiac disease, have served to improve prognosis. However, one of the most homely lessons that has emerged, yet one that has probably had as beneficial value as any, has been the confirmation of the therapeutic usefulness of simple physical rest. Confinement at bed-rest for prolonged intervals during pregnancy has apparently made possible the successful management of patients whose functional cardiac capacity would formerly have been regarded as unequal to the burdens of child-bearing[93].

Although increasing numbers of women are being operated upon during pregnancy for the amelioration of cardiac defects or lesions, it is not yet possible to estimate the influence which such surgery may ultimately have upon obstetric prognosis. In 4 instances of ductus arteriosus observed by the reviewer, operative closure in mid-pregnancy appeared to reverse a deteriorating trend in the patients' circulatory status[116]. Mitral commissurotomy has been accomplished successfuly in at least 6 pregnant women; several of these women had previously suffered severe attacks of pulmonary edema, and consequently would not have been regarded as good "obstetric risks"[2,13,25,84a]. Two instances of successful obstetric results have thus far been recorded in women subjected to the Blalock operation for the tetralogy of Fallot[99,118]. Two patients have also been reported to have delivered safely who had had resection of an aortic coarctation[96,106]. At the present time, however, the operative mortality associated with cardiac surgery undertaken during pregnancy (excepting that done for the closure of a patent ductus arteriosus) is probably as great as the maternal mortality encountered in unoperated cases[49,53].

MANAGEMENT DURING THE ANTEPARTAL PERIOD. 1. *General Measures.* The therapeutic value of limitation of physical activity, and in special instances, of prolonged confinement at bed-rest has been referred to above. It has been pointed out recently that physical activity provokes large increases of cardiac output and not infrequently precipitates congestive failure in the gravid cardiac patient. Because of the underlying increases of cardiac output due to the pregnancy

itself, the danger of failure must be regarded as a potential one throughout the whole course of gestation, but particularly so during the late months[69,105,129].

Similar large increases in cardiac output, and precipitation of heart failure, have been attributed to intercurrent infection and to anemia[64,128]. In addition, the pregnant cardiac patient is said to be particularly vulnerable to the development of eclamptogenic toxemia, the appearance of which considerably increases the gravity of the cardiac condition[58,85]. The hygiene of pregnancy should, therefore, be closely supervised, and should be directed toward avoiding the development of these complications, and to combating them promptly and vigorously when they threaten. A high-protein, low-sodium diet is recommended as a useful adjunct in the prevention of toxemia and congestive failure[22,109,122,150].

2. *Special Measures.* The threat or development of congestive failure at any period of pregnancy is primarily a medical problem, to be managed essentially as it would be in the nonpregnant individual. In 2 pregnant women who failed to respond to standard measures for the relief of acute pulmonary edema, success was recently obtained by the use of ethanol-oxygen inhalations[43]. When acute congestive failure develops prior to the end of the first trimester of gestation, it is recommended that the pregnancy be terminated as soon as the symptoms can be brought under control[9,126,137]. After the first trimester, however, it is said that the maternal welfare will be prejudiced rather than improved by terminating pregnancy prematurely.

The question of corrective cardiac surgery in the gravid woman has been considered briefly in the section on prognosis above.

3. *Therapeutic Interruption of Pregnancy.* In the great majority of pregnant cardiac patients there is no need to recommend this measure. Its advisability is held to be properly open for consideration only in the small number of women who may exhibit one or more of the following phenomena before the end of the first trimester: marked impairment of exercise tolerance; auricular fibrillation; severe bouts of hemoptysis associated with mitral stenosis; evidence of impending or manifest congestive cardiac failure; and associated renal or severe arterial hypertensive disease[9,126,137,39]. Many recent authors would also include coarctation of the aorta as a valid indication for early termination. Whenever possible the decision should be made promptly, inasmuch as the procedures necessary for emptying the uterus become technically more elaborate and hazardous the longer the decision is deferred beyond the second month of gestation. Thus, the simplest and safest method of terminating pregnancy during the first 2 months is by evacuating the uterus *per vaginam*. Thereafter, this method becomes increasingly more difficult and dangerous, and by the end of the third month is probably more hazardous than a resort to abdominal hysterotomy[71]. The latter is by no means a minor procedure, however, and should never be chosen primarily to provide opportunity for a coincidentally desired tubal ligation.

Where religious or other considerations interdict interruption, a strict regimen of bed-rest, preferably in hospital, provides the best available alternative resource for safeguarding the patient's welfare.

MANAGEMENT DURING AND IMMEDIATELY FOLLOWING DELIVERY. 1. *Mode of Delivery.* The trend of recent opinion is that, in maternal cardiac disease, the method by which the patient is to

be delivered should be determined by obstetric rather than medical considerations. It is felt that delivery by the natural passages is to be preferred to cesarean section for all patients excepting those having a coarctation of the aorta, and for those in whom there are definite obstetric indications for operation[5,34,47]. It must be pointed out that this view is based in part upon the fact that comparative mortality rates favor delivery *per vaginam*, and that such comparisons can be misleading[45,51,93]. Nevertheless, most obstetricians would probably agree that a skillfully conducted labor is potentially less taxing upon a handicapped mother than a cesarean section performed with comparable skill. One of the principal hazards of natural labor for the parturient whose circulatory status is in question is the strain attending her efforts during the expulsive, or second stage. It is agreed by all, however, that these efforts should and can be forestalled by judicious and skillful obstetric interference during that stage. Otherwise, there probably are no significant burdens imposed upon her circulation by labor that are not also imposed, in equal if not greater degree, by cesarean section. A number of excellent suggestions for the conduct of labor in maternal heart disease have recently been advanced by Mendelson and Pardee, and by Lund[85,94].

2. *Analgesia and Anesthesia.* The principal consideration here is that adequate oxygenation should be maintained[37,73]. Many satisfactory anesthetic agents and techniques are currently available. In skilled hands, however, it is doubtful whether any single one of them possesses outstanding advantages. Nitrous oxide-oxygen inhalation, supplemented as indicated by the administration of ether, or the use of a local "block," is a useful combination[33]. Spinal and caudal anesthesia tend to "pool" blood in the peripheral vessels of the lower extremities, and may thus serve to forestall the development of pulmonary edema[33]. Their use is to be avoided, however, in the presence of significant arterial hypertension[24].

3. *Precautions Immediately Following Delivery.* The first 48 post-partal hours are fraught with danger for the cardiac parturient. From 20 to 75% of deaths occur during this period[60,143]. Death is usually due to acute congestive cardiac failure, in which pulmonary edema is an early and prominent feature[67].

An analogy between the closure of an arterio-venous fistula and cessation of the utero-placental circulation has been invoked to explain the mechanism of failure in many cases. It is known that sudden surgical occlusion of an arterio-venous shunt may provoke cardiac failure[62]. The closure of the uterine vessels attending the emptying and contraction of that organ presumably forces a mass of blood into the vena cava rather suddenly. If this be so, it is easy to conceive of its overloading the heart and pulmonary circulation, particularly when and if the individual's circulatory competence is already compromised by cardiac disease.

The routine use of oxytocic drugs during and following the third stage is undesirable because these substances are capable of aggravating the above phenomena[14]. In addition to their principal action upon the uterus, they may also exert a constrictor effect upon peripheral vessels which is obviously undesirable[44,152]. It has been shown that they may raise venous pressure even when administered orally[14]. Additional hazards attending their use include their tendency to provoke myocardial ischemia, and ventricular fibrillation in subjects under general anesthesia, or those suffering from coronary insufficiency[36,46,59,117].

EFFECTS OF CHILD-BEARING UPON THE COURSE OF CARDIAC DISEASE. 1. *Early Effects.* In a group of women afflicted with cardiac disorders who had been observed during the course of pregnancy, Jones carefully followed the circulatory status of 70 survivors throughout the first post-partal year[71]. The cardiac functional status of 32 women at the beginning of pregnancy had been rated as Class I (A.H.A.); all but 3 of these women were adjudged to be as well shortly following delivery as they had been before they became pregnant. This was also deemed to be the case for two-thirds of 34 women who had been rated as falling in Class II, but not for 4 survivors from among those who had initially been assigned to Classes III and IV. In some instances, however, the deterioration of cardiac status observed during the early post-partal weeks was not confirmable at later examinations. Improvement in some patients continued to be noted throughout 12 months of observation. The more severely affected women usually required prolonged periods of recuperation.

2. *Late Effects.* Whether one or more pregnancies may shorten the life of a woman having a heart lesion is a question that perennially commands the interest of students of this field [8,38,41,71,110,125]. An examination of the ages at which death occurs in women having rheumatic heart disease suggests that those who have borne children outlive those who have not done so[8,41,66]. It has been pointed out, however, that the nulliparous group probably includes women whose disease has been of such severity as either to have caused death at a youthful age or to have precluded marriage and attempts at child-bearing[8]. Nevertheless, it is of interest that there is no significant difference in the average age at which death occurs among parous women having rheumatic heart disease and among men similarly afflicted[8]. These findings suggest that the circulatory burdens which the gravid state imposes upon a woman having a rheumatic heart lesion do not influence her life-expectancy more appreciably than do other burdens or accidents that she might encounter during comparable 9-month spans of time. The findings, therefore, support clinical impressions that have previously been recorded.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MARCH 17, 1953

Cardiovascular Studies during Air Embolism. T. M. DURANT, M.D., M. J. OPPENHEIMER, M.D., and PETER LYNCH, M.S. (Dept. Physiology and Medicine, Temple Univ. Sch. Med.). In a series of 98 venous air embolism animal experiments, it was demonstrated that there is a significant difference in survival rates between the left side down position and the supine or right side down positions. In the former position, at doses of 7.5 cc./kg., the chances of survival were doubled. This was true whether the animal was in this position at the time of embolism or was turned into it within one minute after injection.

Studies relative to the pathophysiology of venous air embolism showed that there occurs immediately following the air injection an abrupt rise in pulmonary arterial pressure and an equally abrupt fall in systemic arterial pressure associated with an apparent bradycardia due largely to abortive beats which failed to open the aortic valve. In addition to the rise in pulmonary arterial pressure due to peripheral obstruction of this portion of the circulation, there was evidence of an air trap in the right ventricular outflow tract which constituted a further obstructive mechanism, displaceable by appropriate positioning. In surviving animals there occurred a secondary rise in pulmonary arterial pressure, accompanied by polypnea, bigeminal rhythm and apparent bradycardia. The pulmonary venous pressure was found to be elevated in many, but not all, instances. The characteristic respiratory pattern was found to be an initial short period of polypnea or hyperpnea, followed by brief apnea and then a long period of polypnea. The possible mechanisms involved in these circulatory and respiratory disturbances are discussed, and reasons are presented for believing that they depend both on reflex (veratridine-like and pressoreceptor reflexes from the heart and pulmonary vessels) and on mechanical factors.

Cardiac Output by Cuvette Oximeter under Thiopental Sodium Anesthesia. E. M. GREISHEIMER, PH.D., M.D., H. N. BAIER, M.D., and D. W. ELLIS, A.B. (Dept. Physiol., Temple Univ. Sch. of Med.). We have used Wood's cuvette oximeter for the determination of cardiac output in 48 experiments on 10 dogs. This method involves continuous photographic recording of Evans blue dye concentration in whole blood for several seconds following its intravenous injection. The concentration of dye is calculated from the deflection of the galvanometer, by means of a calibration curve made by adding known amounts of dye to the animal's undyed blood.

The great advantage of this method in animals is that a large number of determinations of cardiac output can be made within a short time.

The Brodie method was used for the determination of thiopental sodium concentration in the plasma. The range of thiopental sodium concentrations was 8.4 to 22.4, with an average of 14.92 mg. per liter. The range of cardiac outputs was 1.3 to 4.8, with an

average of 2.96 liters per minute. There is no linear relationship between the thiopental sodium concentration and the cardiac output, as indicated by a correlation coefficient of $+0.316 \pm 0.14$. The heart rate varied from 138 to 228 in different dogs. The range of stroke volume was from 6 (in a hypertensive dog) to 31, with an average of 17.58; it was not correlated with the thiopental sodium concentration. Femoral arterial blood pressure was recorded by means of a strain gauge.

It was noted that the cardiac output increased in each dog during the course of repeated determinations. Since the pulse rate remained unchanged, the increase in cardiac output was associated with an increase in stroke volume. Total peripheral resistance decreased in each dog during the course of the experiment. The systolic blood pressure showed a greater rise than the diastolic, consequently there was a rise in pulse pressure during the experimental procedure.

Hemodynamic Concepts. L. H. PETERSON, M.D., G. CHOQUETTE, M.D., and L. GREENE. (Dept. Physiology, Univ. of Penna. and Dept. Anesthesiology, Univ. Hosp.). This communication concerns the important but poorly understood dynamics of hemodynamics. The only distal force acting upon the aortic valves at end diastole is diastolic pressure since blood velocity is zero (STATIC LOAD). As intraventricular pressure rises, and incrementally exceeds diastolic pressure, these valves will not, however, open. Additional force is necessary to start the arterial column moving before intraventricular blood can be ejected. The forces opposing motion may be called the DYNAMIC LOAD (D_L). Its magnitude depends upon such factors as arterial blood mass, structure and arrangement of vessels, starting friction, and others. Another dynamic factor is IMPACT. As intraventricular pressure rapidly rises, it accelerates its mass against the arterial column causing a sudden initial rise in aortic pressure termed ACCELERATION TRANSIENT (T_R). As flow from ventricle to aorta develops, the opposing forces persist and new ones are added, namely, viscous friction and resistance. A method, previously described, permits controlled study of these dynamic factors. It has been found that when D_L is kept constant, the magnitude of the T_R increases non-linearly, depending upon the acceleration of the injected mass but independent of injected volume. When acceleration remains constant, the T_R rise follows a non-linear U-shaped curve, depending upon the D_L but independent of injected volume. At the trough of this curve the least energy is required to circulate blood. These two independent variables, D_L and T_R, markedly affect the pressure and flow relationships within the circulation in addition to the familiar volume-distensibility ratio. This helps explain the poor correlation between stroke volume and pulse pressure and calls for re-evaluating the concepts of cardiac work and efficiency as well as calculations of "peripheral resistance" based upon cardiac output and blood pressure measurements. Steady blood flow does not obey Poiseuille's law. Now it is seen that pulsatile flow introduces further discrepancies. The magnitude of these discrepancies can be shown by simultaneous comparisons of pulsing, Fick and dye contour measurements.

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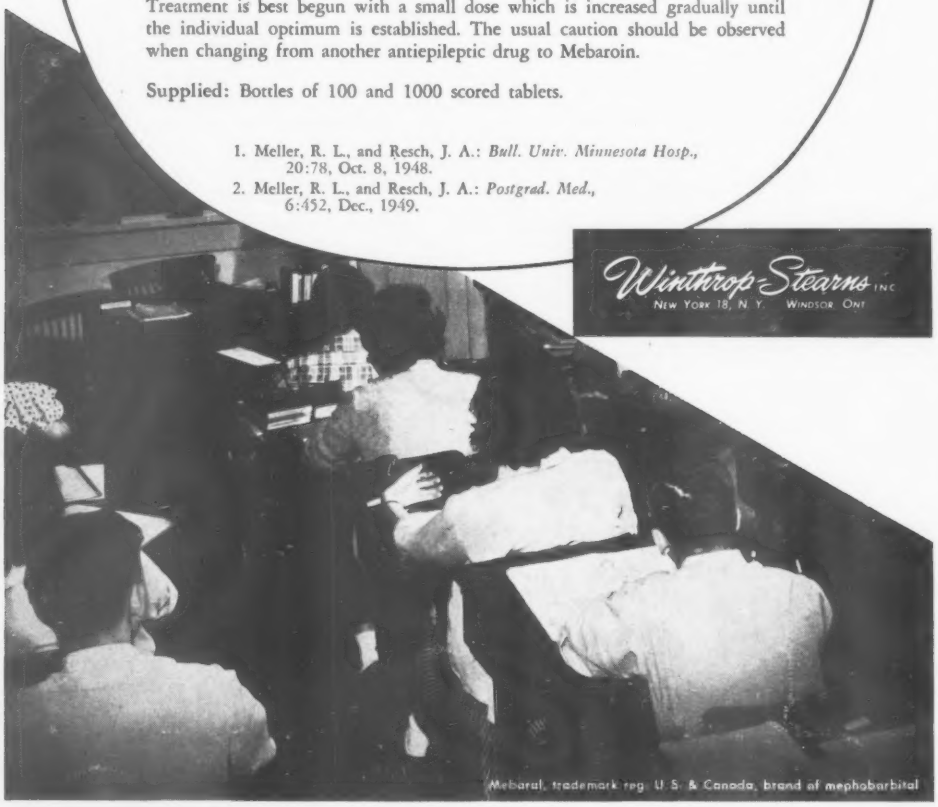

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